Metabolic Fingerprint of Dimethyl Sulfone (DMSO₂) in Microbial–Mammalian Co-metabolism

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S Supporting Information

ABSTRACT: There is growing awareness that intestinal microbiota alters the energy harvesting capacity of the host and regulates metabolism. It has been postulated that intestinal microbiota are able to degrade unabsorbed dietary components and transform xenobiotic compounds. The resulting microbial metabolites derived from the gastrointestinal tract can potentially enter the circulation system, which, in turn, affects host metabolism. Yet, the metabolic capacity of intestinal microbiota and its interaction with mammalian metabolism remains largely unexplored. Here, we review a metabolic pathway that integrates the microbial catabolism of methionine with mammalian metabolism of methanethiol (MT), dimethyl sulfide (DMS), and dimethyl sulfoxide (DMSO), which together provide evidence that supports the microbial origin of dimethyl sulfone (DMSO₂) in the human metabolome. Understanding the pathway of DMSO₂ co-metabolism expands our knowledge of microbial-derived metabolites and motivates future metabolomics-based studies on ascertaining the metabolic consequences of intestinal microbiota on human health, including detoxification processes and sulfur xenobiotic metabolism.

KEYWORDS: DMSO₂, dimethyl sulfone, methylsulfonylmethane, dimethyl sulfoxide, dimethyl sulfide, methanethiol, hydrogen sulfide, intestinal microbiota, metabolism, metabolome

1. INTRODUCTION

The interaction between mammals and their microbial communities has a profound impact on behavior, immunological regulation, energy homeostasis, and metabolism.¹ Previously, much of the scientific literature has focused on comparing the composition of intestinal microbiota between healthy and disease phenotypes, with genetic variation, and under dietary intervention or antibiotic use. Although current molecular techniques based on 16S rRNA screening provides an excellent opportunity to assess the composition of intestinal microbiota, the extent of cross-talk between microbial metabolic and mammalian endogenous pathways is still a work in progress. To date, a number of metabolites have been detected only in conventionally raised animals, but they are absent in germ-free animals.^{2,3} For example, we observed that dimethyl sulfone (DMSO₂) is greatly reduced in the urine of germ-free mice compared to that in their conventionally raised counterparts (Figure 1, unpublished data), suggesting a microbial origin of this compound.

Here, we review the knowledge and provide evidence to support the origin of DMSO₂ through an integrated physiological system involving both mammalian and intestinal microbial activity. We will discuss the biodegradation of dietary methionine by the intestinal microbiota and highlight the bio-conversion from dimethyl sulfide (DMS) to DMSO₂ by the host. We will also address the endogenous methionine transamination

Figure 1. Urinary dimethyl sulfone (DMSO₂) concentration is strongly affected by intestinal microbiota. ¹H NMR-based urinary metabolic analysis revealed a profound signal reduction associated with DMSO₂ (singlet, 3.14 ppm) in germ-free mice (GF mice, green) compared with that in conventionally raised mice (CONV-R, black). A 73.77 μM DMSO₂ standard (≥98.0% pure (Sigma-Aldrich), adjusted to pH 6.86, red) is aligned well after minor shifting downfield (0.002 ppm). The peak at 3.138 is the center of a peak cluster corresponding to ethanolamine.

Received: June 23, 2014

Published: September 23, 2014

pathway and briefly review other external sources of DMSO₂ from diet, supplementation, and the environment. Studying the linkage between DMSO₂ present in the host metabolic profile and its association with intestinal microbial activity will provide a unique opportunity to elucidate the relationship among diet, microbiota, and host metabolic health. This body of knowledge also supports the application of metabolomics-based studies for determining and characterizing microbial enzymatic functionality in the gastrointestinal tract. It will pave the path to a deeper understanding of the mammalian-host metabolic cross-talk that occurs within the colon and continues in a systemic multi-compartmental manner across various tissues and biofluids.

2. THE PRESENCE OF DIMETHYL SULFONE (DMSO₂) IN THE HUMAN METABOLOME

DMSO₂ (also named methylsulfonylmethane, MSM) is a common metabolite found in the human metabolome. In 1966, DMSO₂ was reported to be present in normal human urine,⁴ and more recently, it was detected in blood, cerebrospinal fluid, brain, skin, sweat, and earwax (summarized in Table 1). In cows, DMSO₂ is one of the compounds highly correlated across plasma and milk,⁵ and it is present in the adrenal gland.⁶ Interestingly, DMSO₂ has also been observed in the urine of rats,⁷ bobcats,⁸ and African wild dogs,⁹ as well as the urine and tail gland excretion of red deer.^{10,11}

The correlation between DMSO₂ and age has been demonstrated in several studies. Analysis of the metabolic profile of human skin revealed DMSO₂ as one of the volatile compounds that is more abundant in the skin of elderly people.¹² ¹H NMR analysis on urinary specimens collected from the “Mid-Life in the USA” study (MIDUS II; *n* = 1148; age 35–86 years) suggested that urinary DMSO₂ excretion is also directly associated with age.¹³ However, in a separate study, DMSO₂ and methionine sulfoxide were shown to increase in the urine of elderly individuals (74 ± 1 years) after 14 days of continuous consumption of paracetamol (3 g/day), a common analgesic.¹⁴

3. LINKAGE BETWEEN DIET AND DIMETHYL SULFONE (DMSO₂)

DMSO₂ in the human metabolome can originate from various sources including dietary supplementation. Subjects receiving DMSO₂ as a dietary supplement have the compound rapidly enter the blood and subsequently reach the cerebrospinal fluid.¹⁸ DMSO₂ can also readily transfer across the blood–brain barrier;^{23–25} however, the neurological consequences after supplementation still remain to be investigated.²⁶

The presence of DMSO₂ in human biofluids is highly influenced by diet. For example, in a study involving prostate cancer patients, plasma DMSO₂ concentration was shown to significantly increase after consumption of a rye bran product.²⁷ This may be explained by the high DMSO₂ content in grain^{28,29} or by enhanced intestinal fermentation activity due to fiber consumption. This observation was also observed in rodents, where those fed a high-fat diet (HFD) exhaled lower DMSO₂ and DMS than did rats fed with a standard diet consisting of 77% of energy from grains.³⁰ In gestational sows, a diet formulated with pectin residuals or sugar beet pulp increased serum short-chain fatty acids and DMSO₂ levels compared with that in the barley and wheat-based control diet.³¹

Consumption of onions, which are enriched in sulfoxides, has been shown to increase the concentration of DMSO₂ in the urine of rats.^{32,33} Hens supplemented with cabbage and onion in their

Table 1. Dimethyl Sulfone (DMSO₂) in the Human Metabolome^a

subject	biofluid/tissue	analytical platform	measured dimethyl sulfone (DMSO ₂)	year of publication, ref
healthy subjects (4 men, 4 women, and 3 children)	urine	GC	4–11 mg/day	1966, William et al. ⁴
healthy subjects (<i>n</i> = 22)	urine	¹ H NMR	8.0 μM/mM creatinine (ranging from 1.3 to 49.0)	2013, Bouatra et al. ¹⁵
healthy twin subjects (77 pairs)	plasma and urine	¹ H NMR	DMSO ₂ was detected in both urine and plasma	2011, Nicholson et al. ¹⁶
stage 3–4 chronic kidney disease patients (age = 55 ± 12, 3 women, 7 men), and healthy controls	plasma	¹ H NMR	kidney disease patients: 51 ± 29 μM (mean ± SD); healthy subjects: <30 μM	2013, Mutsaers et al. ¹⁷
patients suspected of having a neurometabolic disease, control patients, and one receiving a dietary supplement containing DMSO ₂ (<i>n</i> = 1),	plasma	¹ H NMR and ¹ H– ¹³ C NMR	control patients: 8.8 ± 7.3 μmol/L (mean ± SD); patient receiving DMSO ₂ supplement: 624 μmol/L	2005, Engelke et al. ¹⁸
patients with severe MAT I/III deficiency (<i>n</i> = 4)	CSF	¹ H NMR and ¹ H– ¹³ C NMR	control patients: 11.3 ± 6.2 μmol/L (mean ± SD); patient receiving DMSO ₂ supplement: 574 μmol/L	
patients with HIV-1 infection (<i>n</i> = 19)	CSF and plasma	¹ H NMR and ¹ H– ¹³ C NMR	plasma: CSF values, each in μmol/L: 7.2; 15.8; 13.1; 20.15	
patients screened for meningitis (<i>n</i> = 50)	CSF and blood plasma	¹ H NMR	the amount of DMSO ₂ is correlated between CSF and blood	2011, Maher et al. ¹⁹
healthy subjects (<i>n</i> = 14)	CSF	¹ H NMR, GC–MS, LC–FTMS	DMSO ₂ was only detected using NMR; 2 ± 1 μM (mean ± SD)	2008, Wishart et al. ²⁰
healthy subjects (<i>n</i> = 25)	dichloromethane extracts of sweat	GC–MS	0.47 ± 0.55 μg/mL	1996, Cork and Park ²¹
healthy subjects (<i>n</i> = 8)	skin	GC–MS	DMSO ₂ was detected	2008, Gallagher et al. ¹²
healthy subjects (<i>n</i> = 8)	earwax (cerumen)	GC–MS	DMSO ₂ was detected in all the subjects	2014, Prokop-Prigge et al. ²²

^aCSF, cerebrospinal fluid; MAT I/III, methionine adenosyltransferase I/III.

diet have higher accumulation of DMSO₂ in their egg yolks compared with that of hens receiving a control meal.³⁴ Similarly, DMSO₂ as well as other sulfur-containing compounds has been reported in human urine following asparagus consumption.^{35,36} Taken together, these observations support the linkage between diet and DMSO₂ in the mammalian metabolome. Below, we describe one possible pathway for its formation that involves the microbial-host co-metabolic pathway for methionine degradation.

4. MICROBIAL–MAMMALIAN CO-METABOLISM OF METHIONINE

Although the microbial–mammalian co-metabolic pathway of DMSO₂ production is poorly understood, there is evidence that links it to the decomposition of methionine by microbiota in the gastrointestinal tract. Methionine that escapes absorption in the small intestine is subjected to absorption and catabolism by bacteria in the colon. Several enzymes exist in colonic bacteria that can convert methionine to methanethiol (MT, also named methylmercaptan) (Figure 2). MT is very reactive and is therefore converted either nonenzymatically to dimethyl disulfide (DMDS) or dimethyl trisulfide (DMTS), or several host enzymes can convert MT to DMS, which is converted to dimethyl sulfoxide (DMSO) and ultimately to DMSO₂ (Figure 2). Elevated MT concentration in feces appears to be largely dependent upon the amount of methionine in the diet. For example, both bovine milk-based and soy-based infant formulas contain more than twice the amount of methionine compared with that in human breast milk, and they also contain sulfate as an additive. Higher concentrations of MT were observed in feces from formula-fed infants compared with that from breast-fed infants.³⁷ Interestingly, individuals consuming a protein supplement that is rich in whey, casein, and lactalbumin experience significantly increased fecal MT, methylpropyl disulfide, and DMTS.³⁸

There is evidence that supports the existence of an altered co-metabolic pathway of methionine in inflammatory bowel disease (IBD) patients. For example, the fecal metagenome of ileal Crohn's disease (CD) patients exhibits a significant increase in genes related to cysteine and methionine metabolism compared with that in healthy subjects.³⁹ Additionally, fecal sulfur-containing compounds (such as MT, DMS, methyl propyl sulfide, and methyl-2-propenyl disulfide) are significantly lower in CD patients compared with that in healthy subjects, whereas H₂S production is higher.^{40,41} Interestingly, Dawiskiba et al. reported that serum DMSO₂ is significantly lower in IBD patients (24 UC and 19 CD patients) compared with that in healthy controls.⁴² It is therefore possible that these intestinal diseases are associated with both a disruption of microbial methionine degradation as well as the host detoxification pathways (discussed in Section 4.2) that reshape the sulfur-compound distribution in the host metabolic profile.

It is important to note that another way to produce DMS is through catabolism of dimethylsulfoniopropionate (DMSP). This metabolite is produced predominantly by marine phytoplankton and can be oxidized to form DMSO and DMSO₂. This bio-conversion has been well-studied in marine microorganisms (reviewed in refs 43 and 44). DMSP-degrading bacteria have been found in marine organisms such as coral,⁴⁵ as well as in the gut of copepod⁴⁶ and the gut of wild plankton-eating fish.⁴⁷ To date, no evidence exists that suggests DMSP is present in the mammalian gut. Therefore, it is possible that dietary methionine is the main precursor of DMS in the mammalian gut.

4.1. Formation of Methanethiol (MT) and Its Oxidized Products via Microbial Methionine Catabolism

Methionine is a sulfur-containing essential amino acid that is primarily provided by the diet. It is an important methyl donor and serves as a precursor for irreversible cysteine synthesis via the transsulfuration pathway. Generally, free methionine is absorbed rapidly in the proximal ileum, but a small portion escapes and flows into colon, where it is not absorbed in a nutritionally significant amount.^{48–50} Indeed, the gastrointestinal tract is the essential site for methionine metabolism and homocysteine production,⁵¹ and the net portal circulation of methionine (48% of intake) tends to be lower than the average of all essential amino acids (56%) after consumption.⁵² This reduction could, in part, be due to the requirement of methionine by intestinal tissues, as nearly 20% of consumed methionine is retained and metabolized within the gastrointestinal tract.⁵³

In contrast to microbial waste byproducts such as ethanol, lactic acid, and citric acid that primarily generate ATP, methionine production in micro-organisms requires energy (ATP). Normally, bacteria are not capable of producing large quantities of methionine due to the strict feedback regulation of L-methionine biosynthetic pathways.^{54,55} It is generally accepted that intestinal microbiota compete with the host for nutrients that have not readily been absorbed. In vitro incubation of methionine with human stool demonstrates its potential as a substrate for intestinal microbial biosynthesis of ammonia, α -ketobutyrate, and possibly MT. Further transformation of α -ketobutyrate leads to production of two short-chain fatty acids, namely, propionate and butyrate⁵⁶ (Figure 2A). The specific intestinal microorganisms that drive this metabolic process, however, remained to be determined.

In mammals, MT can be produced by transamination of methionine to form 4-methylthio-2-oxobutyric acid, followed by the formation of 3-methylthiopropionic acid (Figure 2B, discussed in Section 5). In micro-organisms, the formation of MT can occur in one of two currently known pathways (Figure 2A). One involves deamination of methionine by L-methionine γ -lyase (Mgl), and the other, cystathionine lyase, or C–S lyase. Mgl is absent in mammals but has been demonstrated in plants, parasitic protozoa, as well as numerous bacteria including those in the rumen,⁵⁷ those used in food fermentation, and soil bacteria (Table 2), playing a key function that converts methionine into α -ketobutyrate, MT, and ammonia (reviewed in refs 58–61). Tokoro and colleagues suggest that *mgl* genes and their proteins were likely derived from Archaea by horizontal gene transfer.⁶²

Although none of the lactic acid bacteria (LAB) genomes appear to produce Mgl, the activity of cystathionine lyases has been intensively studied under cheese-ripening conditions (Table 2; also reviewed in ref 63). Indeed, cystathionine lyases from LAB have been shown to provide broad substrate specificities to catalyze α,β - and/or α,γ -elimination, allowing the production of MT from methionine. The efficiency of methionine degradation is highly varied and depends on the specific organisms and environmental conditions.⁶⁴ Of interest, the activity of cystathionine γ -lyase (Cgl, also named cystathionase) is also found in mammals, primarily in the liver, kidney, and blood vessels, and it is primarily responsible for the production of H₂S from cysteine and homocysteine (reviewed in refs 65 and 66).

Another way for MT to be formed is via a two-step degradation pathway that has been demonstrated in lactococcus^{56,88} and other cheese-ripening bacteria.^{89,90} Briefly, 4-methylthio-2-oxobutyric acid (also named α -keto- γ -methyl-thiobutyric acid, KMBA) is first formed via aminotransferase.^{91,92} Then, C–S

Corynebacterium diphtheria,⁹⁶ indicating that the enzymatic reaction that C-S lyase catalyzes may be highly strain-specific. In another path, KMBA can be converted to methional by α -ketoacid decarboxylase (Akd).⁹⁷ It has been proposed that

Table 2. Identified Enzymes with a Function of Converting Methionine to Methanethiol in Bacteria

enzyme	organisms	habitat	ref
cystathionine β -lyase (EC 4.4.1.8)	<i>Escherichia coli</i>		67
	<i>Lactococcus lactis</i> subsp. <i>cremoris</i> B78	cheese-ripening process	68
	<i>Salmonella enterica</i> serovar Typhimurium	mammals and birds	69
	<i>Staphylococcus hemolyticus</i>	human skin	70
cystathionine γ -lyase (EC 4.4.1.1)	<i>Lactobacillus fermentum</i> DT41	cheese-ripening process	71
	<i>Lactococcus lactis</i> subsp. <i>cremoris</i> SK11	cheese-ripening process	72
	<i>Lactobacillus reuteri</i> BR11	guinea pig vagina	73
cystathionine β/γ -lyase	<i>Lactobacillus casei</i>	cheese-ripening process	74
	<i>Lactococcus lactis</i> ssp. <i>cremoris</i> MG1363	cheese-ripening process	75
L-methionine γ -lyase (EC 4.4.1.11)	<i>Aeromonas</i> sp.	lake	58
	<i>Brevibacterium linens</i>	cheese-ripening process	76–78
	<i>Citrobacter freundii</i>	water, soil, food and the intestinal tract of animals and humans	79
	<i>Citrobacter intermedius</i>	sewage sludge	80
	<i>Clostridium sporogenes</i>		81
	<i>Fusobacterium nucleatum</i>	oral cavity	82
	<i>Treponema denticola</i>	oral cavity	83
	<i>Porphyromonas gingivalis</i>	oral cavity	84
	<i>Pseudomonas putida</i> (=ovalis)	soil	85–87

methional (also named 3-methylsulfanylpropanal) degrades to MT by either chemical decomposition or enzymatic conversion;⁸⁹ however, the exact reaction still remains to be determined (Figure 2A). In human oral microbiota, members of the *Fusobacterium*, *Bacteroides*, *Porphyromonas*, and *Eubacterium* genera produce significant amounts of MT after incubation with L-methionine.⁹⁸ *Bacillus subtilis*, a member of the Firmicutes phylum and a common intestinal microbe, can utilize methionine as a sulfur source; however, the utilization of methionine mostly results in formation of homocysteine via the S-adenosylmethionine (SAM) recycling pathway rather than direct production of MT and α -ketobutyrate from methionine.⁹⁹ Although production of KMBA may occur as a part of the methionine salvage pathway, further conversions to MT likely require enzymatic functions from other microorganisms.

It has been established that MT is highly unstable and rapidly oxidizes to DMS, dimethyl disulfide (DMDS), and dimethyl trisulfide (DMTS) in air, soil, and food.^{61,100,101} Specifically, DMDS and DMTS can be produced spontaneously by ascorbate- and metal ion-mediated oxidation of MT.¹⁰¹ MT, along with its downstream oxidized products, has also been observed in bacterial cultures. For example, anaerobic incubation of subgingival microbiota with human serum revealed production of H₂S and MT as well as trace amounts of DMS and DMDS.¹⁰² Addition of L-methionine results in production of MT, DMDS, DMTS, S-methyl thioacetate, and trace methane by *Clostridia*, a ubiquitous bacteria found in aquatic sediments, soils, and the gastrointestinal tract.¹⁰³ Intestinal bacteria such as *Proteus vulgaris*, *P. mirabilis*, *P. rettgeri*, and *Morganella morganii* are capable of utilizing L-methionine in culture media and yield large amounts of MT and DMDS.¹⁰⁴

Halitosis patients that are characterized as overproducers of DMS, determined by measurement of the volatile compounds in the mouth and nose,¹⁰⁵ frequently experience additional gastrointestinal conditions such as abdominal pain, reflux, and vomiting,^{106,107} suggesting that the amount of DMS in the human metabolome is tightly linked with intestinal activity. An examination of the components of human flatus revealed no evidence of DMDS or DMTS but large quantities of DMS, suggesting that, in the GI tract, MT is largely converted to DMS.^{108–110} However, MT, DMS, DMDS, and DMTS have

been identified in the headspace samples above fresh human fecal material.¹¹¹ Interestingly, these volatile compounds failed to be identified in fecal samples of ulcerative colitis (UC) patients who harbor *Campylobacter jejuni* and *C. difficile* in their GI tract, suggesting that there is a MT-mediated toxic effect on host cells that is a result of a disrupted intestinal detoxification capacity associated with the disease-specific phenotype.¹¹¹

4.2. Sulfur Detoxification Pathway

Direct injection of MT into a rodent, or directly incubating with whole blood, results in absorption of free MT, which is either exhaled from the lungs unchanged¹¹² or is oxidized to formic acid and sulfite or sulfate. It can also form protein–S–S–CH₃ and DMS through action of the enzyme thiol S-methyltransferase (EC 2.1.1.9, TSM).¹¹³ In contrast with other mammalian tissues, TSM is highly expressed in the cecal and colon mucosa and converts H₂S to MT or MT to DMS.¹¹⁴ However, Levitt and colleagues suggest that colonic mucosa primarily convert MT to H₂S but not DMS.¹¹⁵ This result agrees with the mammalian methionine transamination pathway proposed by Steele and Benevenga in which MT is converted to H₂S and formaldehyde.¹¹⁶ However, to date, the enzyme methanethiol oxidase (EC 1.8.3.4) that catalyzes the reaction from MT to formaldehyde and H₂S has not been found in mammalian genome but has been characterized only in a few environmental bacteria.^{117–119} Nevertheless, a positive correlation between H₂S and MT concentrations in human flatus has been observed.^{108,110} Although the conversion of MT to formaldehyde and H₂S has been proposed, further studies on characterization of this enzymatic reaction are needed.

H₂S and formaldehyde are known to be extremely toxic compounds. In human mucosal tissue, formaldehyde rapidly oxidizes to formic acid via formaldehyde dehydrogenase (FDH, also known as alcohol dehydrogenase 5, EC 1.2.1.46).^{120,121} Formic acid can enter into the one-carbon unit pool and be released as carbon dioxide.¹²¹ The mucosa can also trigger the detoxification mechanism and rapidly oxidize H₂S to thiosulfate,¹²² which likely involves three enzymatic reactions catalyzed by sulfide:quinone oxidoreductase (SQOR), sulfur dioxygenase (SDO, EC 1.13.11.18), and thiosulfate sulfurtransferase (TSST, also named rhodanese, EC 2.8.1.1).^{123–126} During intestinal inflammation, thiosulfate can be further oxidized to

tetrathionate by nitric oxide (NO) radicals and reactive oxygen species (ROS).¹²⁷ In healthy subjects, fecal H₂S concentration ranges from 0.17 to 3.38 mmol/L (summarized in ref 126) and can be generated from all sulfur-containing compounds such as sulfur amino acids,^{126,128} mucin, cysteine, taurocholate, and sulfate.⁴¹ Free H₂S levels are significantly reduced in the cecum and colon of germ-free mice compared with that in their conventionally raised counterparts, suggesting that microbiota might manage H₂S bioavailability and metabolism.¹²⁹ Together, these studies suggest that the efficiency of the intestinal detoxification is driven by the conversion of MT to less reactive compounds such as DMS, thiosulfate, and others.

4.3. Bioconversion between Dimethyl Sulfide (DMS), Dimethyl Sulfoxide (DMSO), and Dimethyl Sulfone (DMSO₂)

Subcutaneous injection of DMS into rabbits recovered both DMSO and DMSO₂ from urine with approximately 8.6 and 9.8% of the administered dose, respectively;¹³⁰ however, this was not likely due to spontaneous oxidation.¹⁸ In comparison with H₂S and MT, which contain a highly reactive –SH group, DMS is more stable and exists only in the free form in mammals (reviewed in ref 131). Thus, the low urinary elimination rate of DMSO and DMSO₂ after DMS administration may be due to the loss of DMS from breath, slow metabolic conversion among DMS, DMSO, and DMSO₂, or, possibly, the binding of DMSO with tissues. Indeed, administration of DMSO results in a fraction of it binding to plasma protein, followed by skin, liver, diaphragm tissues, and cornea.¹³² DMSO is also able to stimulate formation of DMS, which together may enhance the rate of respiration, uncouple oxidative phosphorylation,¹³³ and increase cytochrome oxidase activity of hepatic mitochondria.¹³⁴ DMSO can also be oxidized to DMSO₂ by hepatic microsomes in the presence of oxygen and either NADPH or NADH¹³² (Figure 2C).

Reduction of DMSO to DMS can occur both in mammalian tissues and intestinal microbiota. Enzymes in the methionine sulfoxide reductase family (EC 1.8.4.11), namely, methionine sulfoxide reductase A (MsrA) and methionine sulfoxide reductase B (MsrB), have shown a broad substrate specificity that can reduce a variety of methyl sulfoxide compounds (reviewed in ref 135). Mammalian MsrA has been shown to catalyze the reduction of DMSO to DMS,¹³⁶ and it is highly expressed in kidney and liver tissues.^{137,138} However, mouse MsrB2 and human MsrB3 enzymes cannot reduce DMSO.¹³⁹ A wide variety of microorganisms found in the gastrointestinal tract are also capable of reducing DMSO to DMS via DMSO reductase (EC 1.8.5.3)^{140–145} or methionine sulfoxide reductase^{146–148} as well as nonspecific reduction of DMSO by the enzyme biotin sulfoxide reductase.^{149,150} Incubation of DMSO with human fecal samples revealed that DMSO was degraded rapidly and was completely gone after 8 h.¹⁵¹ Since DMSO₂ was not detected at any time during the fecal incubation,¹⁵¹ this result suggests that DMSO₂ is not an intermediate in the catabolism of DMSO by intestinal microbiota.

DMSO is readily and efficiently absorbed into the bloodstream via cutaneous, percutaneous, or oral administration (summarized in Table S1). Administration of radioactive DMSO in both humans and animals has shown the compound to be either excreted in urine unchanged or metabolized into DMSO₂. Depending on the dosage, elimination of radioactive DMSO from the blood occurs over a range of 4–48 h and cannot be detected beyond 8 days after its administration. DMSO₂ appears in blood after DMSO ingestion and exhibits a much slower excretion rate than that of DMSO. As described above, DMSO

can be converted to DMS, which can be detected in exhaled air,¹³⁰ and this accounts for about 3% of the administered dose in most species reported (except for calves and cows). Generally, the kidney seems to be the paramount excretory organ for DMSO, whereas excretion via milk and feces is remarkably small.

4.4. Dimethyl Sulfone (DMSO₂): The Stable Metabolic End Product

In 1966, Williams et al. showed that the subcutaneous injection of ¹⁴C-DMSO₂ into rabbits resulted in most of the compound (76%) being excreted in the urine unchanged after 20 days.¹³⁰ Similarly, in 1986, Richmond used guinea pigs to demonstrate that most of the radioactively labeled DMSO₂ was excreted in urine after consumption of ³⁵S-DMSO₂, with none of the radioactivity recovered in feces and 1% accumulated as peptidyl methionine and cysteine.¹⁵² More recently, Otsuki et al. investigated the distribution of radioactivity in rats fed ³⁵S-DMSO₂.¹⁵³ After 7 days of oral gavage, the majority of the ³⁵S radioactivity was recovered in the urine (~70%) and feces (~10%), with the remaining ³⁵S radioactivity in the blood as well as the spleen and hair. It was speculated that a small portion of the administered DMSO₂ might have been incorporated into keratin, a component of hair and nails.¹⁵³ Similarly, Magnuson et al. administered a single oral dose of ³⁵S-DMSO₂ (500 mg/kg) to rats and revealed a recovery rate of 85.8% of the dose in urine and 3% in feces after 120 h, but no quantifiable levels of radioactivity were detected in any tissues.¹⁵⁴ Thus, DMSO₂ represents one of the major end products in the methionine degradation pathway.

5. PRODUCTION OF DIMETHYL SULFONE (DMSO₂) VIA AN ALTERNATIVE PATHWAY

In mammals, the SAM-independent methionine transamination pathway has been previously proposed as an alternative pathway of methionine metabolism which follows a sequential conversion of methionine to 2-keto-4-methylthiobutyric acid, 3-methylthiopropionic acid and ultimately, MT^{116,155,156} (Figure 2B). This catabolic pathway requires a high methionine concentration and does not likely occur under normal circumstances (reviewed in refs 157–160). L-Methionine toxicity and elevated transamination have been found in healthy subjects after oral administration of 0.1 g L-methionine per kg body weight,¹⁶¹ but more intensively seen in methionine adenosyltransferase (MAT) deficient patients and induced by D-methionine administration.¹⁶²

Interestingly, DMSO₂ levels increases considerably after a large flux of methionine administration. For example, in 1975, Tiews et al. showed that oral administration of 50 g D,L-methionine increased DMSO₂ in calf urine.¹⁶³ D,L-methionine supplementation in lactating cows yields more DMS in milk than feeding sulfur or hay alone.¹⁶⁴ Clark and Salsbury showed the oral administration of 60 or 80 g of D,L-methionine resulted in the appearance of DMS in milk. However, no detection can be made with 46 or 40 g of D,L-methionine, or with control capsules.¹⁶⁵ Exhaled DMS increased markedly in normal subjects after intravenous injection of 2 g D-methionine, but not after 500 mg of D-methionine, nor 2 g of L-methionine. The production of DMS is relatively small after administration of 3 g of L-methionine.¹⁶² DMS increased prominently in normal subjects following both oral and parenteral administration of D-methionine, suggesting this route of metabolism might be independent of intestinal microbial activity.¹⁶⁶ Interestingly, MAT I/III deficient patients who have abnormal methionine production exhibit a significantly higher DMSO₂ level in plasma compared to controls.¹⁸ DMS concentration is also

elevated in these individual's breath, blood, and urine compared with normal values (breath: 5.86 ± 0.11 nM vs 0.34 ± 0.03 nM; blood: 73 and 96 nM vs 3–6 nM; urine: 400 nM vs 2 nM, respectively).¹⁶⁷

6. DIMETHYL SULFONE (DMSO₂) FROM EXTERNAL SOURCES

Apart from microbial enzymatic reactions and endogenous metabolism of methionine, DMSO₂ can directly enter the physiological DMSO₂ pool from external sources, which can contribute to the overall host metabolic phenotype. Organic sulfur compounds, including DMS, DMSO, and DMSO₂, are part of a global sulfur cycle in the marine ocean–atmosphere system.^{168,169} DMSO and DMSO₂ are water-soluble, existing naturally in the earth's surface water, seawater, rainwater, and air; however, the presence of DMSO₂ is not as abundant as DMSO.^{170–173} DMS, DMSO, and DMSO₂ also accumulate in edible green algae, *Capsosiphon fulvescens*, constituting a dietary source in seaweed-consuming individuals.¹⁷⁴

DMSO and DMSO₂ are naturally occurring organic sulfur compounds commonly found in a variety of fruits, vegetables, grains, and beverages.^{28,29,175,176} DMSO content in food likely originates from DMS oxidation during commercial processing.¹⁷⁶ Unlike DMSO₂, which is odorless, DMS is extensively found in nature and is responsible for the characteristic odor and flavor in numerous food products. Pearson et al. examined 18 different types of commonly consumed fresh and processed foods and determined that food containing DMSO has at least a trace amount of DMSO₂.¹⁷⁵ Milk is the only exception, where the levels of DMSO₂ greatly exceed that of DMSO, which may suggest the production of DMSO₂ in milk comes from animal metabolism.¹⁷⁵ Several studies report the presence of DMS, DMDS, DMTS, and DMSO₂ in cooked beef.^{177,178}

DMSO₂ in dairy and meat products is also likely influenced by agricultural practices and food processing. DMSO₂ was found in a higher concentration in milk¹⁷⁹ and meat profiles^{180,181} of cows that were pasture-raised in contrast to that in those that were indoor grain-fed, which can be directly related to the amount of dietary methionine.¹⁸¹ Ultra-high-temperature treatment promotes the reduction of DMSO₂ in raw milk, but it favors the formation of H₂S, MT, carbon disulfide, DMDS, DMTS, and DMSO.¹⁸² In wine, DMSO₂ formation is not dependent on temperature and acidity, but it increases over time in the presence of oxygen.¹⁸³

7. CONCLUDING REMARKS

There is a growing body of evidence supporting the linkage between the presence of DMSO₂ and intestinal microbial degradation of methionine from the diet. With clear evidence that the human metabolome persistently contains DMSO₂ under normal conditions, we demonstrate a metabolic pathway that is initiated with microbial metabolism of methionine, followed by generation of DMS in the colon, host bioconversion between DMS and DMSO₂, and eventually secretion of DMSO₂, a more stable compound, in urine. Although DMSO₂ and its precursor DMSO have shown therapeutic promise in *in vitro* and animal studies (reviewed in refs 184–186), the biological significance of DMSO₂ under healthy and various disease phenotypes still remains to be demonstrated. Furthermore, the measurement of DMSO₂ in urine and serum often exhibits great within-individual variation,¹⁶ which may be explained by temporary dietary changes or the volatility of DMSO₂. Furthermore, because DMSO₂ is

highly water-soluble, the amount of DMSO₂ extracted using organic solvents is low.

One of the limitations of the pathway presented here is the lack of definitive enzymatic functions (Figure 2, reactions labeled with question mark); thus, more studies are needed to validate these reactions. It is important to mention that a study in 1975 by Salsbury and Merricks reported the production of MT after incubating S-methyl cysteine with rumen fluid,¹⁸⁷ suggesting that S-methyl cysteine may be another substrate involved in the production of MT by bacteria. Interestingly, increased concentrations of H₂S, MT, and allyl mercaptan were detected in the oral cavity after chewing garlic (high in S-methyl cysteine), which was subsequently reduced by more than 80% after immediate brushing of the teeth and mouth, suggesting that oral microbiota, at least in part, are involved in generating these compounds.¹⁸⁸ Trace amounts of DMSO₂, allyl methyl sulfide, and allylmercaptan were detected in skin samples after garlic intake that were absent before.¹⁸⁹ However, the details of the enzymatic conversion between S-methyl cysteine and MT still remained to be determined.

It has been established that the composition and diversity of intestinal microbiota can be modified by diet.¹⁹⁰ Therefore, the linkage between dietary factors and metabolic health has to be defined by the extension of enzymatic capacity of the intestinal microbiota induced by the diet. To date, there is still a considerable lack of understanding of the biochemistry and the enzymatic capabilities of intestinal microbiota and its interaction with mammalian metabolism. Extensive work is needed to assign potential microbial-derived metabolites in a systematic and integrative network that traces the impact of the intestinal microbiota on the human metabolic phenotype.

This review extends and complements prior knowledge concerning how diet influences microbial metabolic function, paving an outlook on future studies aimed at the role of the metabolic fingerprint as indicative of a specific intestinal fermentation activity. The current review supports the application of metabolomics analysis on measurement of downstream products of intestinal microbial activity. This new body of knowledge allows for the tailoring of immediate and future studies on understanding the metabolic interaction between host and intestinal microbiota.

■ ASSOCIATED CONTENT

📄 Supporting Information

Elimination and excretion patterns of dimethyl sulfoxide (DMSO), dimethyl sulfone (DMSO₂), and dimethyl sulfide (DMS) after administration of DMSO. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are particularly grateful to Drs. Ann Spevacek, Helen Raybould, and Maria Marco as well as Alice Martinic, Jennie Sotelo, and Maaria Kortensniemi for helpful discussion and comments.

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