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Review

Endogenous Roles of Mammalian Flavin-Containing Monooxygenases

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Abstract: Flavin-containing monooxygenases (FMOs) catalyze the oxygenation of numerous foreign chemicals. This review considers the roles of FMOs in the metabolism of endogenous substrates and in physiological processes, and focuses on FMOs of human and mouse. Tyramine, phenethylamine, trimethylamine, cysteamine, methionine, lipoic acid and lipoamide have been identified as endogenous or dietary-derived substrates of FMOs in vitro. However, with the exception of trimethylamine, the role of FMOs in the metabolism of these compounds in vivo is unclear. The use, as experimental models, of knockout-mouse lines deficient in various *Fmo* genes has revealed previously unsuspected roles for FMOs in endogenous metabolic processes. FMO1 has been identified as a novel regulator of energy balance that acts to promote metabolic efficiency, and also as being involved in the biosynthesis of taurine, by catalyzing the *S*-oxygenation of hypotaurine. FMO5 has been identified as a regulator of metabolic ageing and glucose homeostasis that apparently acts by sensing or responding to gut bacteria. Thus, FMOs do not function only as xenobiotic-metabolizing enzymes and there is a risk that exposure to drugs and environmental chemicals that are substrates or inducers of FMOs would perturb the endogenous functions of these enzymes.

Keywords: cholesterol; energy balance; FMO; glucose; human; hypotaurine; insulin; mouse; taurine; weight

1. Introduction

Flavin-containing monooxygenases (FMOs; EC 1.14.13.8) are best known for their role in catalyzing the oxidative metabolism of numerous foreign chemicals, which include therapeutic drugs and environmental pollutants [1–4]. This review, however, considers the roles of FMOs in the metabolism of endogenous substrates and in physiological processes. It focuses on FMOs of human and mouse and how the use of genetically modified mouse models are contributing to our understanding of the endogenous roles of FMOs.

The human genome encodes five functional *FMO* genes, designated *FMO1*, *2*, *3*, *4* and *5* [5–7]. Four of these genes, *FMOs 1*, *2*, *3* and *4* are located within a 245-kb cluster on chromosome 1, in the region q24.3 [7]. An additional *FMO* gene, *FMO6P*, located within this cluster, does not produce a correctly processed mRNA and, thus, is classified as a pseudogene [8]. The *FMO5* gene is located closer to the centromere in the region 1q21.1 [7]. A second cluster of *FMO* genes, located at 1q24.2, consists of five pseudogenes, designated *FMO7P*, *8P*, *9P*, *10P* and *11P* [7]. In the mouse genome, five *Fmo* genes, *Fmo1*, *2*, *3*, *4* and *6*, which are the orthologues of the corresponding human genes, are similarly clustered on Chromosome 1 [7]. The *Fmo5* gene, which is orthologous to human *FMO5*, is located on mouse Chromosome 3 [7]. On mouse Chromosome 1 ~3.5 Mb from the main *Fmo* gene cluster there is a second cluster of *Fmo* genes containing three genes, *Fmo9*, *Fmo12* and *Fmo13* [7]. Based on

their sequences, *Fmo6*, *Fmo9*, *Fmo12* and *Fmo13* appear to be functional genes; however, the functional capabilities of their protein products have not been analysed.

2. Developmental Stage- and Tissue-Specific Regulation of Expression of FMOs in Human and Mouse

In both human and mouse, each *FMO* gene has a distinct pattern of developmental stage- and tissue-specific expression. However, there are marked differences between the two species (Table 1). Adult humans do not express *FMO1* in liver because in this tissue expression of *FMO1* is switched off after birth [9–11]. Transfection experiments revealed that LINEs (long-interspersed nuclear element)-1 like elements located upstream of the core hepatic promoter of the human *FMO1* gene repress transcription of the gene [12]. Expression of *FMO1* in human extra-hepatic tissues such as kidney [10,13,14] and small intestine [13] is under the control of alternative downstream promoters P1 and P2 [7,12]. In contrast, in mouse the *Fmo1* gene is highly expressed in adult liver [15,16]. The gene is also expressed in several other tissues in mouse, including kidney, lung [16], white adipose tissue [17] and brain, a tissue in which it is the most highly expressed FMO [16].

Table 1. Major sites of expression of flavin-containing monooxygenases (FMOs) in adult human and mouse tissues.

	Human	Mouse Male	Mouse Female
FMO1	Kidney	Liver, Lung, Kidney	Liver, Lung, Kidney
FMO2	Lung	Lung	Lung
FMO3	Liver	-	Liver
FMO5	Liver, Gastrointestinal tract	Liver, Gastrointestinal tract	Liver, Gastrointestinal tract

The main site of expression in both human and mouse of the gene encoding FMO2 is the lung [2,16,18] (Table 1). Most humans, however, are homozygous for a genetic variant of *FMO2*, c.1414C > T[p.(Gln472*)], which introduces a premature translation stop codon. The resulting allele, *FMO2*2A*, encodes a polypeptide of 471 amino-acid residues that lacks the C-terminal 64 residues and is catalytically inactive [19]. Some individuals of recent African descent possess the ancestral allele, *FMO2*1*, which encodes a full-length polypeptide of 535 amino-acid residues (FMO2.1) that is catalytically active [19]. In sub-Saharan Africa the ancestral gene is widespread and can attain a frequency of up to 26% in some regions, with up to 50% of individuals possessing at least one *FMO2*1* allele [20].

The liver is the main site of expression of *FMO3* in humans [10] (Table 1). It is also expressed in skin [21], pancreas and in adrenal medulla and cortex [7]. In the liver, *FMO3* gene expression is activated within the first two years after birth and increases to reach a maximum in adulthood [11]. Apart from a decline during menstruation [22,23], the expression of *FMO3* is similar in females and males. In mouse, however, there is a marked difference in expression of the *Fmo3* gene in liver of females and males [16,24]: in females the gene is expressed throughout adulthood, whereas in males, the expression declines from three weeks of age and is undetectable by five to six weeks of age. In contrast, in lung the *Fmo3* gene is expressed in both genders throughout adulthood [16].

The expression of *FMO4* is very low in both human and mouse [2,7,10,16].

In both human and mouse the gene encoding FMO5 is most highly expressed in the liver [2,16] (Table 1). The gene is also expressed in both species in the intestinal tract including the stomach and small and large intestine [2,7,25,26]. In humans, the gene encoding FMO5 is also expressed in pancreas [7] and in mouse in the kidney [16].

3. Catalytic Mechanism

Our understanding of the catalytic mechanism of FMOs is based on the early work of Dan Ziegler and colleagues [27–29]. FMOs contain FAD, as a prosthetic group, and, for catalysis, require NADPH as a cofactor and oxygen as a co-substrate. Preferred substrates contain, as their site of oxygenation, a soft nucleophilic heteroatom, typically nitrogen or sulfur, but in some cases phosphorus or selenium. The mechanism of action of FMOs is unusual and differs in several aspects from other monooxygenases such as cytochromes P450 [30]. FMOs can activate oxygen in the form of a stable C4a-hydroperoxyflavin in the absence of bound substrate (Figure 1). FMOs accept electrons directly from their bound co-factor, NADPH, and do not require an accessory protein to assist in the oxygenation of a substrate. FMOs oxygenate substrates via a two-electron mechanism that usually results in the production of readily excretable detoxification products.

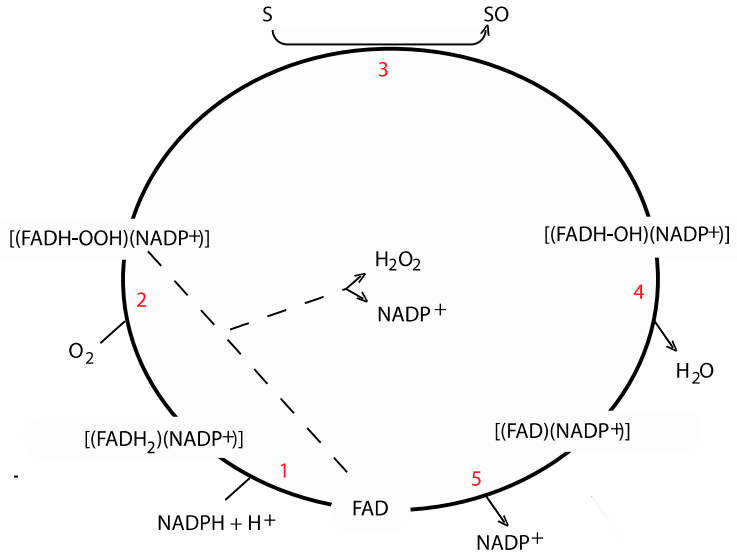

Figure 1. Representation of the catalytic cycle of mammalian FMOs. 1. NADPH binds to the enzyme and reduces FAD to $FADH_2$. 2. Molecular oxygen binds and is reduced, forming C4a-hydroperoxyflavin, which is stabilized by $NADP^+$. 3. Substrate (S) is oxygenated leaving the prosthetic group in the form of C4a-hydroflavin. 4. Water is released, and FAD is reformed. 5. $NADP^+$ is released. Uncoupling of the cycle produces hydrogen peroxide from the C4a-hydroperoxyflavin, and $NADP^+$ is released to reform FAD (dashed lines). Based on [29,31].

The rate-limiting steps of FMO-catalyzed reactions are the breakdown of FADH-OH to release water and the release of $NADP^+$. As both of these steps occur after the oxygenation of substrate, the structure of the substrate usually has little effect on the catalytic constant (k_{cat}) and the K_M for the substrate is the key determinant of the specificity constant (k_{cat}/K_M). FMOs do not form enzyme-substrate complexes in the classical Michaelis–Menten manner. Consequently, K_M reflects the ease with which a substrate gains access to the active site. Access of the substrate to the active site is determined by its size, shape and charge [28,29,32]. Molecules that are uncharged or have a single positive charge are the best substrates, whereas those with more than one positive charge, zwitterions or most compounds with a negative charge are poor substrates.

Human FMO5, however, has been identified as a Baeyer–Villiger monooxygenase [33], capable of catalyzing the oxidation of carbonyl compounds, forming an ester by insertion of an oxygen atom into a carbon-carbon bond adjacent to the carbonyl group [34].

FMOs can also moonlight as NADPH oxidases: the catalytic cycle uncoupling to produce hydrogen peroxide, with the release of $NADP^+$ [31] (Figure 1). This has been shown for FMOs 1, 2, 3 [31] and 5 [34]. As hydrogen peroxide is recognized as a signaling molecule [35], its production may represent a potential endogenous role for FMOs.

FMO1 and FMO3 can accommodate a broad range of substrates, some of which are common to both enzymes (reviewed in [1,4]). Most of the identified substrates of FMO1 and FMO3 are tertiary amines, which are *N*-oxygenated to form the *N*-oxide, or sulfides, which are *S*-oxygenated to the *S*-oxide. The substrate range of FMO2 and FMO5 is more restricted, with FMO5 displaying little or no activity towards compounds that are good substrates of other FMOs [1,4,36]. However, with the identification of human FMO5 as a Baeyer–Villiger monooxygenase [33], it is likely that more substrates of the enzyme will be identified, possibly including endogenous compounds.

4. Endogenous Substrates of FMOs

Charge restriction is an important factor in excluding almost all small endogenous compounds from the active site of FMOs and, thus, preventing their oxygenation by the activated enzymes [28,29]. However, there are exceptions, and analysis of the catalytic activity of microsomes or recombinantly expressed enzymes in vitro has identified a number of endogenous or dietary-derived compounds as substrates of FMOs.

4.1. Tyramine and Phenethylamine

The biogenic amines tyramine and phenethylamine are classified as trace amines. They act as sympathomimetic agents, mimicking the effects of endogenous monoamine neurotransmitters such as epinephrine, norepinephrine, serotonin and dopamine [37]. Tyramine and phenethylamine bind to the intracellular trace amine-associated receptor 1 (TAAR1) [38]. This activates signaling via protein kinase A and C pathways, resulting in the phosphorylation of the dopamine transporter, which either internalizes the transporter or causes it to operate in reverse [39]. The effect is to promote release and prevent re-uptake of monoamine neurotransmitters by presynaptic neurons. Phenethylamine can also inhibit reuptake of neurotransmitters by vesicular monoamine transporter 2 (VMAT2) [39,40]. Tyramine cannot cross the blood–brain barrier, so acts on the peripheral nervous system, causing vasoconstriction and an increase in blood pressure [37]. Phenethylamine, however, can cross the blood–brain barrier and acts as a central nervous system stimulant [41].

Tyramine and phenethylamine are dietary derived, but are also biosynthesized in mammals from the amino acids tyrosine and phenylalanine, respectively, by decarboxylation catalyzed by aromatic L-amino acid decarboxylase [42]. Tyramine and phenethylamine are metabolized mainly by monoamine oxidases [42]. Both compounds can also be *N*-oxygenated by human FMO3 to the *N*-hydroxylamine metabolite, then, via a second, stereoselective, *N*-oxygenation to the di-*N*-hydroxylamine, followed by spontaneous loss of water to form the *trans*-oxime [43,44] (Figure 2a,b). The K_M of human FMO3 for tyramine is 0.22 mM and for tyramine *N*-hydroxylamine is 0.49 mM [43]. The K_M of human FMO3 for phenethylamine is 90 μM and for phenethylamine *N*-hydroxylamine is 63 μM [44]. The hydroxylamine and *trans*-oxime metabolites of tyramine and phenethylamine have very poor affinity for receptors for dopamine and serotonin and for the dopamine transporter, indicating that FMO3 mediated metabolism of the compounds represents a detoxification process that terminates the biological activity of the parent compounds [43,44].

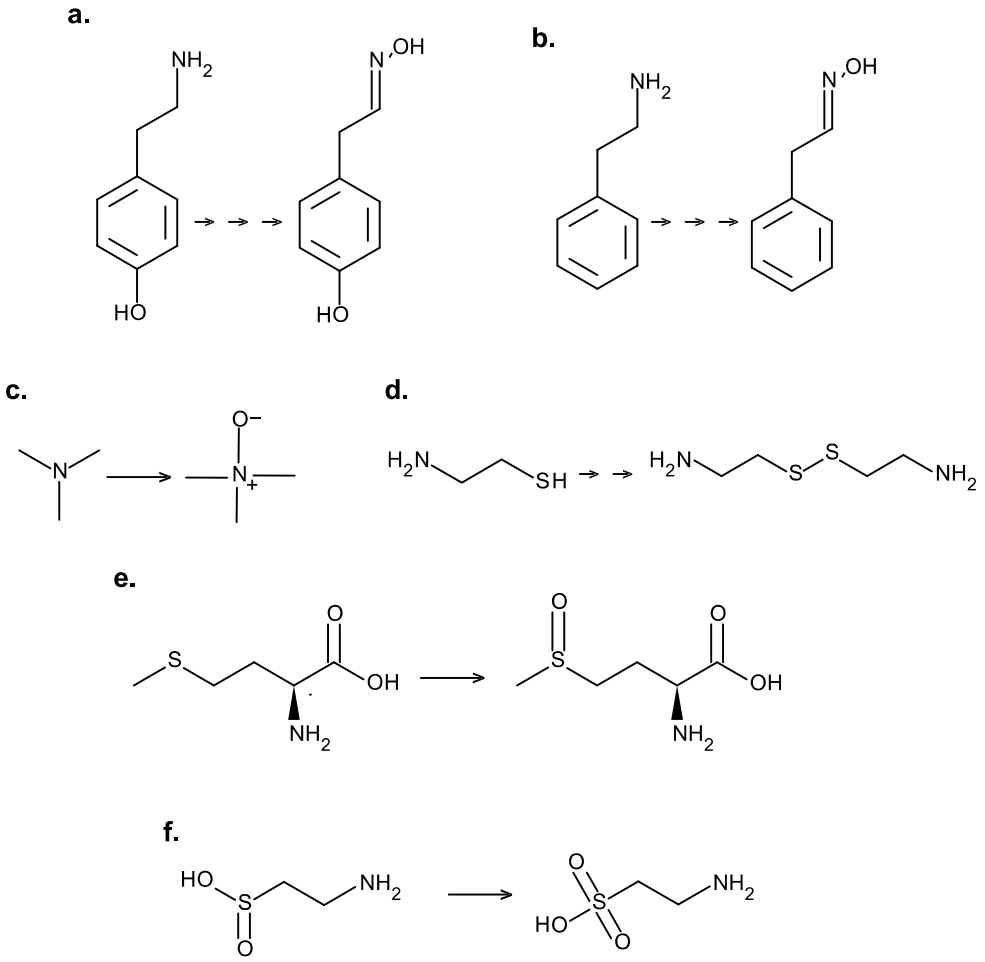

Figure 2. Structures of endogenous substrates of FMOs and of the final products of their FMO-catalyzed oxygenation. (**a**) Tyramine and *trans*-4-hydroxyphenethyl oxime. (**b**) Phenethylamine and *trans*-phenethyl oxime. (**c**) Trimethylamine and trimethylamine *N*-oxide. (**d**) Cysteamine and cystamine. (**e**) Methionine and methionine sulfoxide. (**f**) Hypotaurine and taurine. Multiple arrows indicate that multiple reactions are required to obtain the final product from the initial substrate.

4.2. Trimethylamine

Trimethylamine is a highly volatile tertiary amine that has a smell characteristic of rotten fish [45,46]. It is derived from the metabolism of dietary components, such as choline, carnitine, betaine, ergothioneine and trimethylamine *N*-oxide, by the action of gut bacteria [47] (reviewed in [48]). The free amine is absorbed into the bloodstream and transported to the liver, where it is converted to trimethylamine *N*-oxide, which is non-odorous and the oxygenated product is then excreted in the urine [49,50]. The oxygenation of trimethylamine to its *N*-oxide (Figure 2c) is selectively catalyzed by FMO3, with a K_M of 28 μM and an apparent k_{cat} of >30 min^{-1} [51]. The role of FMO3 in metabolizing a product of bacterial action in the gut identifies FMO3 as a protein that plays an important role in host-microbiome metabolic interaction [48].

Individuals who are homozygous or compound heterozygous for rare variants of the *FMO3* gene that abolish or severely affect either the amount of protein produced or the activity of FMO3 are unable to effectively metabolize trimethylamine to its *N*-oxide [52–54]. Consequently, they excrete excessive amounts of the odorous amine in their breath, sweat and urine, which imparts a pungent ammoniac odor reminiscent of rotten fish [55], and suffer from the inherited disorder primary trimethylaminuria (OMIM 602079) (reviewed in [56–59]). More than 40 genetic variants of *FMO3* that cause trimethylaminuria have been identified (reviewed in [3,57,60,61]) and a human *FMO3* locus-specific database, which catalogues genetic variants of *FMO3*, has been established [62,63].

Individuals affected with trimethylaminuria have no overt physical symptoms and appear normal and healthy. However, owing to the unpleasant odor that is associated with the disorder affected individuals often suffer from psychological problems, which can have a severe effect on quality of life, giving rise to a variety of mental health problems and, in extreme cases, suicidal tendencies [56]. Because of their odor, those afflicted with the disorder are often subjected to discrimination and ridicule. Trimethylamine is a chemical for which the human nose has great sensitivity. Some individuals can detect concentrations of the molecule as low as 1 part in 10^9. Trimethylamine is detected via its interaction with TAAR5, a receptor for tertiary amines located in the olfactory epithelium [64].

In addition to defective FMO3 causing the inherited disorder primary trimethylaminuria, trimethylamine *N*-oxide, the product of FMO3-catalyzed oxygenation of trimethylamine, has been associated with several disease states (reviewed in [48,65]). In particular, elevated plasma concentrations of trimethylamine *N*-oxide have been implicated as a risk factor for cardiovascular disease [66–70]. However, other studies report a lack of correlation of trimethylamine *N*-oxide with biomarkers of cardiovascular disease [71] or that it has a protective effect [72]. The identification of trimethylamine *N*-oxide as a causative factor of cardiovascular disease remains controversial.

Many of the studies that implicate trimethylamine *N*-oxide as a causative factor of cardiovascular disease involve chronic administration to mice of precursors of trimethylamine in amounts far higher than those in normal diets. In contrast, a study of males and females of two mouse strains (C57BL/6J and CD-1) and two knockout-mouse lines (*Fmo1*$^{-/-}$, *Fmo2*$^{-/-}$, *Fmo4*$^{-/-}$, which lacks genes encoding FMO1, FMO2 and FMO4; and *Fmo5*$^{-/-}$, in which the gene encoding FMO5 is disrupted) fed a standard chow diet found that plasma cholesterol concentration was negatively correlated with production and urinary concentration of trimethylamine *N*-oxide and that there was no correlation between an index of atherosclerosis and either trimethylamine *N*-oxide production or its urinary concentration [73]. Thus, under normal dietary conditions trimethylamine *N*-oxide does not act as a proatherogenic molecule.

The potential physiological roles of trimethylamine *N*-oxide have been the subject of a number of reviews that present evidence for and against the molecule being detrimental for health [74–77].

4.3. Cysteamine

In mammals, cysteamine is derived from degradation of coenzyme A via the intermediate pantetheine. Cysteamine is a precursor for the biosynthesis of the neurotransmitter hypotaurine in a reaction catalyzed by cysteamine dioxygenase (EC 1.13.11.19) [78]. Cysteamine is used for the treatment of cystinosis, a lysosomal storage disorder caused by mutations in the *CTNS* gene that disrupt the function of the encoded protein cystinosin, which transports cystine from lysosomes into the cytosol [79]. Consequently, cystine accumulates and crystallizes in lysosomes, causing damage, particularly in the kidney and eye [80]. Cysteamine converts cystine into cysteine and cysteine-cysteamine disulfide, which can exit lysosomes, thus preventing further damage [79]. Cysteamine is also a potential therapeutic agent for neurodegenerative and neuropsychiatric disorders, including Huntington's disease [81,82] and Parkinson's disease [83].

Cysteamine can be *S*-oxygenated to the disulfide (cystamine) (Figure 2d) by both pig FMO1 [84], with a K_M of 120 μM, and human FMO2, with a K_M of 175 μM [1]. The physiological significance of cysteamine *S*-oxygenation is not known. However, cysteamine, at concentrations as low as 39 μM, is toxic to cells [85], and FMO-catalyzed oxygenation of cysteamine may represent a detoxification mechanism.

4.4. Methionine

Methionine is an essential amino acid and, thus, not biosynthesized in humans or in other animals. It can be converted, in a reaction catalyzed by methionine adenosyltransferase, into *S*-adenosylmethionine [86], a cofactor that serves as a methyl donor in many methyltransferase reactions, being converted into *S*-adenosylhomocysteine in the process. Methionine is an intermediate

in the biosynthesis of a number of important physiological molecules, including cysteine, carnitine, taurine, lecithin, phosphatidylcholine and other phospholipids.

Methionine can be converted to methionine sulfoxide (Figure 2e) by FMO3. However, as the K_M of human FMO3 for methionine is ~4 mM [87], the physiological significance of the reaction is unclear. In addition to the low-affinity FMO3 activity, human and rabbit liver microsomes contain a high-affinity methionine *S*-oxidase activity with a K_M in the μM range [87]. However, the enzyme responsible for the high-affinity activity was not identified.

4.5. Lipoic Acid and Lipoamide

Lipoic acid is biosynthesized in the mitochondrial matrix, via a series of reactions that culminates in the transfer of a lipoate residue, via an amide bond (lipoamide), to E2 subunits of 2-oxoacid dehydrogenases and to the E3-binding protein of the pyruvate dehydrogenase complex (PDHC) [88].

Lipoic acid functions as a prosthetic group in five multienzyme complexes (reviewed in [88]). Four of these are 2-oxoacid (α-ketoacid) dehydrogenase complexes. Of these, two are involved in the citric acid cycle: PDHC, which catalyzes the conversion of pyruvate to acetyl-CoA, and the α-ketoglutarate dehydrogenase complex, which catalyzes the conversion of α-ketoglutarate to succinyl CoA. The other two are involved in amino acid metabolism: the branched-chain α-ketoacid dehydrogenase complex, which catalyzes decarboxylation of ketoacids in the catabolism of the branched-chain amino acids leucine, isoleucine and valine, and the 2-oxoadipate dehydrogenase complex, which catalyzes the decarboxylation of 2-oxoadipate to glutaryl-CoA in the catabolism of lysine, hydroxylysine and tryptophan. The fifth complex, the glycine cleavage system, catalyzes the decarboxylation of glycine coupled with the addition of a methylene group to tetrahydrofolate to form 5,10-methylene tetrahydrofolate, an important cofactor in nucleic acid synthesis.

Although intracellular concentrations of free, non-protein-bound lipoic acid are likely to be low, unbound lipoic acid may have physiological roles. For instance, lipoic acid has been shown to activate the insulin signaling cascade [89], increase GLUT4 translocation to cell membranes and increase glucose uptake into adipose and muscle cells in culture [90,91]. Lipoic acid is also involved in the activation of antioxidant signaling pathways. Interaction of lipoic acid with Kelch-like ECH-associated protein 1 (Keap1) in the cytosol causes release of the transcription factor nuclear factor E2-related factor 2 (Nrf2) [92], which translocates to the nucleus and upregulates the expression of genes encoding mediators of the antioxidant response by binding to antioxidant response elements (AREs) in their promoters.

FMO can catalyze the *S*-oxygenation of lipoic acid and lipoamide, with human FMO2 having a K_M of 71 μM for *S*-oxygenation of lipoic acid [1]. However, the structures of the oxygenated products were not reported. Degradation of lipoic acid in vivo involves mitochondrial β-oxidation followed by *S*-methylation and sulfoxidation of the methyl sulfide [93]. It is not known whether FMOs are able to catalyze sulfoxidation of the methyl sulfide metabolites of lipoic acid.

5. Evidence for Involvement of FMOs in Endogenous Metabolic Processes

There is evidence from studies in animals and/or cell culture systems for the potential involvement of FMOs in various endogenous metabolic processes. However, the evidence is indirect and sometimes contradictory.

5.1. FMO1

Hepatic FMO1 activity is higher in insulin-deficient streptozotocin-induced diabetic rats than in control animals, but returned to normal upon administration of insulin, suggesting that FMO1 is under the control of insulin [94]. However, insulin had no effect on the activity of FMO1 in the livers of control rats [94].

5.2. FMO3

Studies on mice have identified potential roles for FMO3 in cholesterol metabolism and reverse cholesterol transport [67,95] and in glucose and lipid homeostasis [96]. Evidence concerning the role of FMO3 in glucose homeostasis is contradictory. One study identified FMO3 as a target for down-regulation by insulin [97], indicating that the protein had a detrimental effect. However, another study found that FMO3 acted independently of the insulin-signaling pathway to reduce lipid-induced endoplasmic reticulum stress, which has been implicated in obesity-induced insulin resistance, and to down-regulate expression of the rate-limiting gluconeogenic enzyme phosphoenoylpyruvate carboxykinase (PEPCK) [98], and thus had a beneficial effect on glucose homeostasis.

When considering the results of experiments on mice it is important to recognize that the expression of hepatic FMO3 is influenced by gender: after five to six weeks of age, the *Fmo3* gene is no longer expressed in the livers of males, but continues to be expressed in the livers of females [16,24]. This concern also applies to mouse hepatocyte cultures, as the cells retain a memory of the gender of the animal from which they were isolated [99].

5.3. FMO5

Expression of *FMO5* is increased in response to the hormones progesterone [100] and testosterone [99]. It is also increased by rifampicin [99,101] and hyperforin [102], ligands of the pregnane X receptor, activation of which has been proposed to contribute to type 2 diabetes [103]. In apparent contradiction, expression of the *FMO5* gene was found to be down-regulated in the livers of individuals with type 2 diabetes [104].

A combined quantitative trait locus and transcriptomic approach in rats identified FMO5 as being important for the functioning of brown adipose tissue [105].

In mouse livers, FMO5 mRNA and protein display a diurnal rhythm with amounts increasing during the light phase and decreasing during the dark phase [106]. The Baeyer–Villiger monooxygenase activity of FMO5 displayed the same diurnal rhythm. The use of knockout-mouse lines and primary mouse hepatocytes showed that FMO5 expression was up- and down-regulated respectively by the clock proteins BMAL1 (brain and muscle Arnt-like protein-1) and E4bp4 (E4 promoter-binding protein 4) [106]. It is not yet clear how the diurnal rhythm of FMO5 influences its role in endogenous metabolism.

6. The Use of Knockout-Mouse Lines to Identify Endogenous Roles of FMOs

The development of knockout-mouse lines in which various *Fmo* genes have been deleted or disrupted provides valuable experimental models that allow a more direct approach for the identification of endogenous roles of FMOs.

A knockout-mouse line (*Fmo1*$^{-/-}$, *Fmo2*$^{-/-}$, *Fmo4*$^{-/-}$) that lacks the genes encoding FMO1, FMO2 and FMO4 [107–109] was produced so that the profile of FMOs in the liver of female mice better reflects that in the liver of adult humans [3,4,7]. Initially the knockout-mouse line was used to investigate the roles of FMOs in the metabolism of drugs in vivo. Use of the mouse line identified the role of FMO1 in the production of the *N*-oxide of the anti-depressant imipramine [109,110] and of FMO2 in the metabolism of the anti-tubercular ethionamide [111].

6.1. Identification of FMO1 as a Novel Regulator of Energy Balance

The mouse line was subsequently used as an experimental model for the investigation of the roles of FMOs in endogenous metabolism. When fed a standard chow diet, *Fmo1*$^{-/-}$, *Fmo2*$^{-/-}$, *Fmo4*$^{-/-}$ mice appear healthy, but they are leaner and, despite a similar consumption of food, weigh less and have smaller fat depots, particularly epididymal fat pads, than their wild-type counterparts [17]. The reduced amount of epididymal fat in the knockout mice is due to a decrease in the size, not of the number of adipocytes. There is no difference between the *Fmo1*$^{-/-}$, *Fmo2*$^{-/-}$, *Fmo4*$^{-/-}$ mice and wild-type mice in adipogenesis, or in lipid import into, export from, or synthesis in, white adipose

tissue (WAT). The diminished storage of fat in WAT of the knockout mice is not accompanied by an increase in the storage of fat in either liver or brown adipose tissue.

The smaller amounts of WAT in *Fmo1*$^{-/-}$, *Fmo2*$^{-/-}$, *Fmo4*$^{-/-}$ mice are secondary to enhanced whole-body energy expenditure. The rate of fatty acid β-oxidation in skeletal muscle is higher in *Fmo1*$^{-/-}$, *Fmo2*$^{-/-}$, *Fmo4*$^{-/-}$ mice than in wild-type animals, which is likely to contribute to the enhanced whole-body energy expenditure and to depletion of stores of triglycerides in WAT of the knockout animals.

There is evidence for the operation within WAT of the *Fmo1*$^{-/-}$, *Fmo2*$^{-/-}$, *Fmo4*$^{-/-}$ mice of an internal fuel cycle, in which triglycerides are broken down to glycerol and non-esterified fatty acids, which are then re-esterified to reform triglycerides. The cycle is termed 'futile' as each turn consumes energy, which would contribute to the higher energy expenditure of the knockout mice.

The FMO4 protein has not been detected in vivo in humans or mice. In addition, the majority of humans lack functional FMO2 [19,112] with no apparent physiological consequences. It is therefore unlikely that either of these proteins plays an important role in endogenous metabolic processes in mammals. In contrast, the *Fmo1* gene is highly expressed in metabolically active tissues, including liver, kidney, WAT and brown adipose tissue. Thus, as discussed by Veeravalli et al. (2014) [17], of the three genes deleted in the *Fmo1*$^{-/-}$, *Fmo2*$^{-/-}$, *Fmo4*$^{-/-}$ mouse, it is the deletion of *Fmo1* that most likely underlies the metabolic phenotype. The results identify the FMO1 protein as a regulator of energy balance and a promoter of metabolic efficiency.

6.2. FMO1 Catalyzes the Formation of Taurine from Hypotaurine

Taurine, one of the most abundant amino acids in mammalian tissues, is obtained from the diet and can also be biosynthesized from cysteic acid [113] or hypotaurine [114]. The enzyme that catalyzes the de novo synthesis of taurine from hypotaurine was initially identified as an NAD-dependent hypotaurine dehydrogenase [115], but this was subsequently shown to be incorrect [116] and the identity of the enzyme that catalyzes the formation of taurine from hypotaurine has remained elusive.

Analysis, by one-dimensional ^{1}H NMR spectroscopy, revealed that the urine of *Fmo1*$^{-/-}$, *Fmo2*$^{-/-}$, *Fmo4*$^{-/-}$ mice contained markedly higher concentrations of hypotaurine than did that of wild-type mice [117]. Conversely, the urinary concentration of taurine was higher in wild-type than in *Fmo1*$^{-/-}$, *Fmo2*$^{-/-}$, *Fmo4*$^{-/-}$ mice. The accumulation of hypotaurine and the deficit of taurine in the urine of *Fmo1*$^{-/-}$, *Fmo2*$^{-/-}$, *Fmo4*$^{-/-}$ mice suggested that an FMO was involved in the production of taurine from hypotaurine. Assays in vitro of human FMOs revealed that FMO1 catalyzed the conversion of hypotaurine to taurine [117] (Figure 2f). The FMO1-catalyzed *S*-oxygenation of hypotaurine had a k_{cat} of 55 min^{-1} and a K_M of 4 mM [117]. Although the K_M is high, the in vivo results from the *Fmo1*$^{-/-}$, *Fmo2*$^{-/-}$, *Fmo4*$^{-/-}$ mice confirm the physiological relevance of FMO1 for the production of taurine.

Taurine is an organic osmolyte involved in regulation of cell volume [118]. In addition, it is involved in the formation of bile salts [118] and in the modulation of the intracellular concentration of calcium [119]. In neurological and ocular tissues, it has been reported to have cytoprotective and developmental roles [120]. Taurine deficiency is therefore thought to play a role in several pathological conditions. Hypotaurine is also an organic osmolyte and cytoprotective agent [121] and acts as an antioxidant which scavenges highly reactive hydroxyl radicals [122].

6.3. Identification of Endogenous Roles for FMO5

FMO5 displays little or no activity towards drug substrates of other FMOs, and, in humans, the *FMO5* gene, in common with *FMO1*, but in marked contrast to *FMO2* and *FMO3*, displays very little genetic variation [3,123]. Consequently, an endogenous role for FMO5 has long been suspected. To investigate this, a mouse line (*Fmo5*$^{-/-}$) was produced in which the gene encoding FMO5 is disrupted [124].

Fmo5$^{-/-}$ mice appear healthy, but display a lean phenotype, which is age related [124]. As they age wild-type mice continue to gain weight and to increase their WAT depots and plasma concentration

of cholesterol. In contrast, as they age, *Fmo5*$^{-/-}$ mice gain little weight, despite eating more than wild-type mice. Their fat-to-body-weight ratio and plasma cholesterol remain similar to those of 10-week-old animals. The *Fmo5*$^{-/-}$ mice exhibit no increase in physical activity and their lean phenotype is associated with enhanced whole-body energy expenditure, most of which is due to higher resting energy expenditure.

The depleted triglycerides stores of *Fmo5*$^{-/-}$ male mice can be explained in part by a higher rate of fatty acid β-oxidation in epididymal WAT. Interestingly, the rate of fatty acid β-oxidation in skeletal muscle is lower in *Fmo5*$^{-/-}$ mice than in wild-type mice, suggesting a switch in *Fmo5*$^{-/-}$ mice to an increased use of carbohydrate as fuel in this tissue. In the dark phase, the time at which mice are most active, the respiratory exchange ratio (RER) is higher in *Fmo5*$^{-/-}$ mice than in wild-type mice. This increase in RER supports the increased use of carbohydrate as a fuel source, possibly in response to diminished lipid stores in WAT.

Proteomic analysis of liver identified five proteins that are down regulated in *Fmo5*$^{-/-}$ mice (Figure 3). Three play roles in carbohydrate metabolism: aldolase B (fructose bis-phosphate aldolase B) and ketohexokinase (fructokinase), which are involved in glucose and fructose metabolism, and glycerol 3-phosphate dehydrogenase (GPD1), which is important for production of NAD^+, for use in glycolysis, and of glycerol 3-phosphate, which can be combined with fatty acids to produce triglycerides. The other two down-regulated proteins are involved in lipid or cholesterol biosynthesis: cytosolic malic enzyme 1 (ME1), which catalyzes the oxidative decarboxylation of malate to pyruvate, in the process producing NADPH for use in lipid and cholesterol biosynthesis, and β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) synthase 1, which catalyzes the first committed step in isoprenoid biosynthesis; modulation of the activity of HMG-CoA synthase 1 has been shown to influence cholesterol biosynthesis [125,126]. Down regulation of GPD1, ME1 and HMG-CoA synthase 1 would moderate the biosynthesis of triglycerides and cholesterol, providing a potential explanation for the reduced fat deposits and lower plasma cholesterol concentration of *Fmo5*$^{-/-}$ mice.

Wild-type mice, as they age, display an increase in their plasma concentrations of both glucose and insulin [26]. In contrast, *Fmo5*$^{-/-}$ mice maintain the plasma concentrations of glucose and insulin characteristic of young animals and, thus, require less insulin to maintain the lower glucose concentration [26]. In comparison with wild-type mice, *Fmo5*$^{-/-}$ mice have better glucose tolerance, and greater insulin sensitivity. Therefore, in the absence of FMO5, glucose tolerance and insulin sensitivity are improved.

Wild-type mice, when fed a high-fat diet, gain weight, and their plasma concentrations of glucose and insulin increase, and their glucose tolerance and insulin sensitivity decrease (Figure 4A). In contrast, *Fmo5*$^{-/-}$ mice, when fed a high-fat diet, do not gain weight and there is no reduction in their insulin sensitivity [26].

As the *Fmo5*$^{-/-}$ mice age or when fed a high-fat diet, the composition of the bacteria in their gut changed to that which is associated with an obesogenic state. However, these changes in gut flora did not result in weight gain and had no effect on plasma concentrations of glucose and insulin, or on glucose tolerance and insulin sensitivity [26] (Figure 4A). Treatment with antibiotics for two weeks had a dramatic effect on wild-type mice fed a high-fat diet, reversing the effect of the diet on plasma concentrations of glucose and insulin and on glucose tolerance, but had no effect on these metabolic parameters in *Fmo5*$^{-/-}$ mice [26]. The metabolic phenotype of *Fmo5*$^{-/-}$ mice is therefore independent of diet and the gut microbiome and is determined solely by host genotype.

The metabolic phenotype of *Fmo5*$^{-/-}$ mice is similar to that of germ-free mice, suggesting that in *Fmo5*$^{-/-}$ mice gut flora are 'invisible' to the host and that FMO5 has a role in sensing or responding to gut bacteria. Consistent with this, FMO5 is expressed in the epithelial lining throughout the gastro-intestinal tract and there is evidence that *Fmo5*$^{-/-}$ mice have an impairment in the production in the colon of the active, monomeric form of resistin-like molecule β (RELMβ) [26] (Figure 4B), a mucosecretagogue and inflammatory mediator [127].

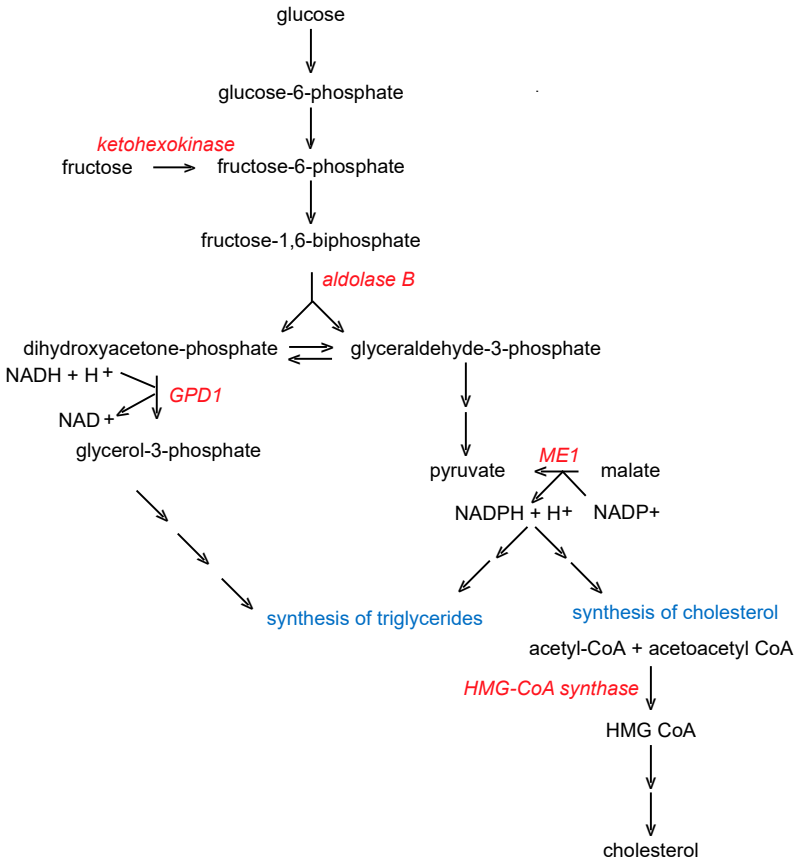

Figure 3. Reactions catalyzed by the proteins down-regulated in the liver of *Fmo5*$^{-/-}$ mice and the metabolic pathways in which they are involved. Down-regulated proteins are shown in red. GPD1, glycerol 3-phosphate dehydrogenase; ME1, cytosolic malic enzyme 1; HMG-CoA synthase, β-hydroxy-β-methylglutaryl-CoA synthase 1.

In comparison with wild-type mice, *Fmo5*$^{-/-}$ mice have lower concentrations of tumor necrosis factor α (TNFα) in plasma and of complement component 3 (C3) in epididymal WAT [26] (Figure 4B), indicating that FMO5 has a deleterious effect on systemic inflammatory tone. RELMβ promotes the synthesis and release of TNFα from macrophages [128], suggesting that the effect of FMO5 on the concentration of TNFα may be mediated by its influence on the production of monomeric RELMβ (Figure 4B). In addition, TNFα plays a role in regulating the expression of C3 [129] (Figure 4B). Both TNFα [130] and C3 [131–133] have detrimental effects on insulin sensitivity (Figure 4B). Thus, the lower concentrations of TNFα in plasma and of C3 in WAT would contribute to the enhanced whole-body insulin sensitivity of *Fmo5*$^{-/-}$ mice.

In wild-type mice, the *Fmo5* gene is not expressed in WAT [124], indicating that the marked effects on WAT metabolic processes of disruption of the *Fmo5* gene are indirect.

The metabolic phenotype of *Fmo5*$^{-/-}$ mice indicates that FMO5 regulates metabolic ageing via pleiotropic effects, including increasing cholesterol and lipid synthesis. FMO5 is also involved in the regulation of body weight and in glucose disposal and insulin sensitivity, apparently via its role in sensing or responding to gut bacteria.

In humans, the expression of FMO5 varies among individuals [36] and the protein is inducible by certain drugs, natural products and hormones [100–102] (Section 5.3). The role of FMO5 in endogenous metabolism indicates that variation in the abundance of the protein may affect weight gain and insulin sensitivity and thus influence metabolic health. Even though an absence of FMO5 is today associated with a healthy metabolic profile its presence during evolution may have conferred an advantage,

by contributing to the capacity of mammals, including humans, to accumulate fat and increase body weight, particularly during times of food scarcity.

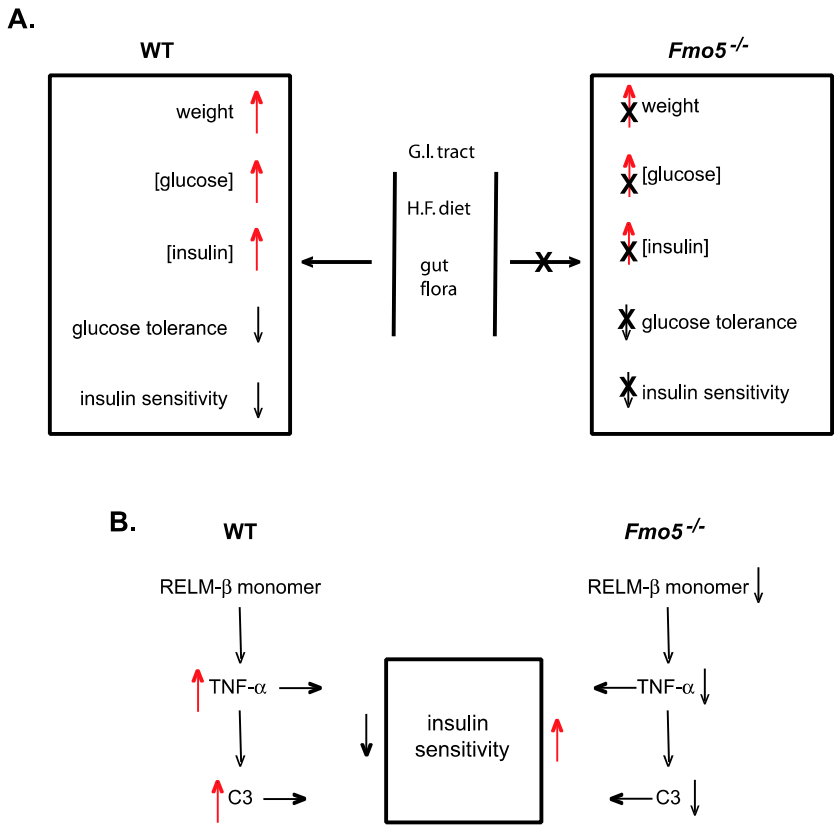

Figure 4. Summary of metabolic differences between wild-type and *Fmo5*$^{-/-}$ mice. (**A**) Differences in the response of wild-type (WT) and *Fmo5*$^{-/-}$ mice to a high-fat diet and changes in gut flora. [Glucose] and [insulin], plasma concentrations of glucose and insulin, respectively; G.I. tract, gastro-intestinal tract; H.F. diet, high-fat diet. Vertical arrows indicate an increase (up, red) or decrease (down, black). Horizontal arrows indicate an influence. A cross over a vertical arrow indicates that the effect (increase or decrease) does not occur. A cross over a horizontal arrow indicates that the influence is negated. (**B**) Differences between wild-type (WT) and *Fmo5*$^{-/-}$ mice in the production of the active, monomeric form of resistin-like molecule β (RELMβ) in the colon, and in the concentrations of tumor necrosis factor α (TNF-α) in plasma and of complement component 3 (C3) in epididymal WAT. Vertical arrows alongside TNF-α, C3 or the central box indicate an increase (up, red) or decrease (down, black), respectively.

7. Conclusions

FMOs catalyze the oxygenation of a range of foreign chemicals, including many therapeutic drugs. In contrast, almost all small endogenous molecules are excluded from the active site of FMOs, as a consequence of the charges they bear. However, analysis of the catalytic activity of microsomes and recombinantly expressed enzymes has identified a small number of endogenous or dietary-derived compounds as substrates of FMO. FMO3 can catalyze oxygenation of the trace amines tyramine and phenethylamine, the dietary-derived compound trimethylamine and the amino acid methionine, whereas FMO1 and FMO2 can catalyze oxygenation of cysteamine, lipoic acid and lipoamide. With the exception of trimethylamine, it is not known whether FMOs play a significant role in the metabolism of these compounds in vivo.

Recently, hypotaurine has been identified as a substrate of human FMO1 and studies of a knockout-mouse line confirmed the physiological relevance of FMO1-catalyzed *S*-oxygenation of hypotaurine for the biosynthesis of taurine.

The development of knockout-mouse lines in which various *Fmo* genes have been disrupted provides experimental models that allow a direct approach for identifying endogenous roles of FMOs. Investigation of the metabolic phenotype of such knockout-mouse lines has revealed previously unsuspected roles for FMO1 and FMO5 in the regulation of endogenous metabolic processes. FMO1 has been identified as a novel regulator of energy balance that acts to promote metabolic efficiency, and FMO5 as a regulator of metabolic ageing and glucose homeostasis that apparently acts by sensing or responding to gut bacteria. The endogenous substrates with which FMO1 and FMO5 interact to exert their physiological effects have not been identified.

The identification of FMO1 and FMO5 as metabolic regulators means that FMOs can no longer be considered exclusively as xenobiotic-metabolizing enzymes and the potential for competition between foreign and endogenous substrates for available enzyme or, in the case of FMO5, induction by therapeutic agents, has implications for human health.

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