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Review Article

Flavin-containing Monooxygenases in the Brain and their Involvement in Neurodegeneration and Aging

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Abstract

Flavin-containing monooxygenases (FMOs) catalyze the oxygenation of a diverse range of sulfur or nitrogen-containing xenobiotics. Recently accumulated evidence has demonstrated the roles of FMOs in physiological and pathological conditions, including neurodegeneration and aging. However, the mechanisms underlying their functions are poorly understood. In this review, we summarize the expression and localization of FMOs in the brain, the endogenous chemicals and xenobiotics metabolized by FMOs, and the consequences of FMO deficiency. The understanding of FMOs activity in the brain is important for fully elucidating the roles of FMOs in pathological mechanisms.

Introduction

Flavin-containing monooxygenases (FMOs) constitute a family of microsomal enzymes catalyzing the oxidation of nucleophilic heteroatom-containing xenobiotics.[1] They oxygenate the sulfur or nitrogen atoms in chemicals with soft nucleophiles.[2] FMOs are involved in the pathogenic process of trimethylaminuria, atherosclerosis, cardiovascular disease, diabetes, and metabolic disorders.[3–6] In recent years, the involvement of FMOs in neurodegeneration and aging has emerged,[7] but the underlying mechanisms have not been elucidated. In this review, we summarize the expression and localization of FMOs in the brain, the endogenous chemicals and xenobiotics metabolized by FMOs in the brain, and the consequences of FMO deficiency.

FMO

FMO (EC 1.14.13.8) was first described by Ziegler *et al.*[8,9] Humans possess five functional FMO genes, designated *FMO1–5*. *FMO1–4* are clustered on chromosome 1 q24.3, and *FMO5* is located at 1q21.1.[10,11] Numerous allelic variants, including approximately 20 of human *FMO1,* have been reported.[12]

Mammalian FMOs are NADPH- and oxygen-dependent microsomal monooxygenases that usually metabolize nitrogen- and sulfur-containing compounds.[1,13,14] The catalytic mechanism involves a first step in which FAD undergoes a 2-electron reduction by NADPH. The reduced flavin then reacts rapidly with molecular oxygen to form peroxyflavin. This nucleophilic attack by the substrate on FADOOH results in the transfer of one atom of molecular oxygen to the substrate with another contributing to the formation of water.

Trimethylaminuria is a currently confirmed rare inherited metabolic disorder associated with abnormal amounts of dietary-derived trimethylamine and is caused by the mutations in FMO3.[15,16]

Emerging roles of FMOs in neurodegeneration and aging

Amyotrophic lateral sclerosis

Association between FMOs and amyotrophic lateral sclerosis (ALS) has been widely reported although some reports are contradictory. Malaspina *et al.*[17] reported an 80% reduction in *FMO1* mRNA levels in the spinal cord of sporadic ALS patients. In contrast, Gagliardi *et al.*[18] observed greater *FMO1* expression in the spinal cord and brain stem of ALS patients compared with that in healthy controls. Gagliardi *et al.*[19] found that the mRNA levels of all FMOs except for *FMO3* were up-regulated in the brain of SOD1-mutated (G93A) ALS mice compared with control mice, with the highest increase in *FMO1* in the spinal cord and brainstem. Cereda *et al.*[12] found a significantly elevated frequency of *FMO1* single nucleotide polymorphisms in female sporadic ALS patients, further indicating that specific allelic variants of *FMO1* might be associated with ALS development.

Keywords: Flavin-containing monooxygenases (FMOs); Brain; Expression; Location; Substrates; Deficiency; Neurodegeneration and aging.

Abbreviations: ALS, amyotrophic lateral sclerosis; CYP, cytochrome P450; FMOs, flavin-containing monooxygenases; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; PTP, 4-phenyl-1,2,3,6-tetrahydropyridine; TMAO, trimethylamine N-oxide; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; FAD, flavin adenine dinucleotide.

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Parkinsonism

Accumulating evidence indicates a relationship between FMOs and parkinsonism. The FMO gene cluster is associated with the volume of the lentiform nucleus, which is a physiological marker associated with Parkinson's disease (PD). Nicotine can be N-oxidized by FMOs and can reduce oxidative stress and neuro-inflammation in the brain and improve synaptic plasticity and neuronal survival of dopaminergic (DA) neurons, thereby benefiting PD patients.[20,21] MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a neurotoxin and its toxic metabolite 1-methyl-4-phenylpyridinium (MPP^+) can kill DA neurons and elicit parkinsonism. MPTP can be deactivated by FMOs into a harmless metabolite in the brain (discussed in detail in the section, *Endogenous Substances and Xenobiotics Oxygenated by FMOs in the Brain*). In addition, we have shown that FMO1 deficiency promotes neuroinflammation that affects the survival of DA neurons in mice. The levels of *FMO1* mRNA transcripts decreased in a rotenone model of parkinsonism, accompanied by decreasing levels of *parkin* mRNA transcripts and increased Caspase-3 activation.[22,23]

Aging

FMO1–5 have all been reported to be transcriptionally activated in classical mouse models of longevity, including calorie restriction, growth hormone/insulin-like growth factor 1 signaling disruption, and rapamycin treatment.[7] The expression of *FMO3* is up-regulated in the liver of a variety of longevity mouse models.[24–27] However, up-regulation of *FMO3* expression in hepatocytes of murine models has recently been shown to prevent or reverse hepatic aging. This mimicked calorie restriction and the associated mechanism is probably attributed to the promotion of autophagy.[28] Furthermore, feeding with a normal diet significantly down-regulated *FMO1* mRNA transcripts in mice in an age-dependent manner,[29] indicating that reduced *FMO1* expression contributes to the progression of aging. However, the specific mechanism underlying its role is still unknown.

The expression and localization of FMOs in the brain

The mRNAs of mammalian FMO isoforms can be detected in different organs, including the liver, kidney, lung, and brain.[30] FMOs are active in human, rat, mouse, rabbit, hamster, and guinea pig brains.[31–37] Here we mainly review FMO activity in mouse and human brains.

Mouse brain

In an adult mouse brain, *FMO1* and *5* are the most abundant FMOs, as detected using isoform-specific antisense RNA probes.[30] *FMO1* mRNA transcripts are observed in neurons of the cerebrum and the choroid plexus while *FMO5* mRNA transcripts are only detected in neurons of the cerebrum. FMO expression in astrocytes remains controversial. Janmohamed *et al.*[30] reported no detectable FMO activity *in vivo*, while Di Monte *et al.*[38] detected FMO activity in primary cultures of mouse astrocytes.

In the neonatal brain, the most abundant FMO mRNA transcripts are *FMO1,* and their level drops by approximately 80% at 8 weeks of age. The levels of *FMO5* mRNA transcripts are 70% of *FMO1* in neonates and are similar to that of *FMO1* in 3-, 5- and 8-week-old mouse brains. *FMO2*, *3,* and *4* mRNA transcripts are present at relatively low levels; approximately <1 molecule/cell.

Human brain

Zhang *et al.*[34] examined the developmental expression of FMOs in 60 human brain samples detecting all *FMO1–5* mRNA transcripts. FMO mRNA levels in the brain were much lower than that in other tissues, about less than 1% compared with the most abundant tissues observed (i.e., *FMO1* in the kidney, *FMO2* in the lung, and *FMO3* and *5* in the liver). *FMO1* is the only subtype to be down-regulated in adult human brains, while the amounts of other FMO mRNA transcripts in human brains remain similar among different age groups. Few studies have reported the expression of FMOs in human brains. Cashman *et al.*[39] found that FMO3 was selectively expressed in the substantia nigra of human brains by immunohistochemistry.

Endogenous substances and xenobiotics oxygenated by FMOs in the brain

Endogenous substances

FMO catalyzes the N- and S-oxygenation of several endogenous substances, including phenethylamine, tyramine, amphetamine, and trimethylamine that can be converted by FMO in the brain with clinical significance.[40] S-oxygenation of hypotaurine by FMO1 contributes to the production of taurine in the brain, which possesses neurotransmitter, antioxidant, and anti-inflammatory functions.[41]

Xenobiotics

FMO oxidizes particular xenobiotics in the brain. Nicotine, which is abundant in tobacco smoke and can diminish oxidative stress and neuroinflammation in the brain, is hydroxylated by CYP2A6 and undergoes glucuronidation by UDP-glucuronosyl transferases and oxidation by FMO.[21,42,43] Several psychoactive drugs, *e.g.* imipramine, chlorpromazine, and fluoxetine, are N- or S-oxygenated by FMO in both rat and human brains.[31,32,44] Imipramine causes greater sedation in wild-type animals compared with *FMO1*-null mice, probably because imipramine N-oxide is produced in the wild-type brain and a higher concentration of desipramine is produced in the *FMO1*-null brain.[45]

A typical xenobiotic oxidized by FMO is the pro-neurotoxin, MPTP, which can lead to DA neuron degeneration and parkinsonism in humans.[46–48] MPTP in the brain is rapidly converted to the toxic MPP^+[49,50] by monoamine oxidase B[51,52] or CYP (marmoset CYP2D6 and human CYP1A2).[47,49,53] However, MPTP can be deactivated to 4-phenyl-1,2,3,6-tetrahydropyridine (PTP) and MPTP N-oxide that is non-neurotoxic, by CYP2D6 and FMO (Fig. 1).[53–55] The concentrations of MPP^+ in *Suncus* brains after a single intraperitoneal administration of MPTP were markedly higher than that in rats, probably because of the lack of FMO activity in *Suncus* brains.[56] FMO1 and 3 may contribute to this detoxification. MPTP N-oxygenation in human brain microsomes was consistently catalyzed by human FMO1 and 3.[53]

What are the consequences of FMO deficiency?

Genetic deficiency of FMOs has several consequences. FMO1 deficiency promotes neuroinflammation that affects the survival of DA neurons in C57BL/6N mice.[23] Mice with FMO1, 2, and 4 deficiency exhibit a lean phenotype and enhanced resting energy expenditure, those with FMO1 deficiency most likely underlying the metabolic phenotype.[57] FMO3 is a target of insulin and knockdown of FMO3 expression in insulin-resistant mice improves glucose tolerance.[6] Knockdown of FMO3 expression in the liver of low-density lipoprotein receptor-knockout mice leads to decreased

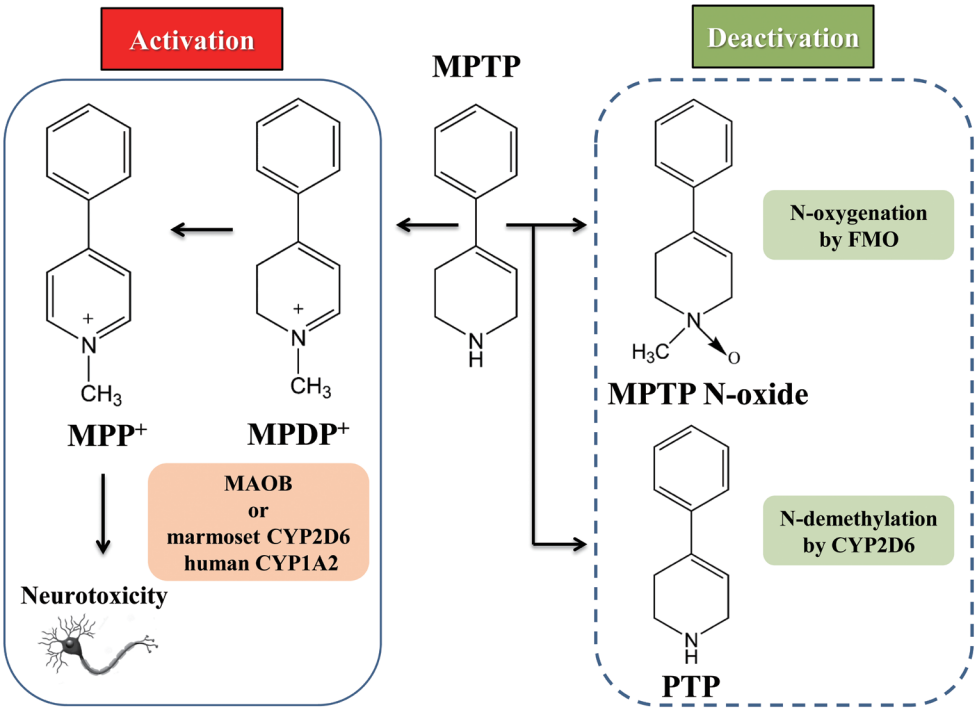

Fig. 1. Metabolic activation and deactivation of MPTP. Activation: MPTP was rapidly converted to the toxic metabolite MPP^+ through the intermediate $MPDP^+$ once in the brain mediated by monoamine oxidase B or CYP (marmoset CYP2D6 and human CYP1A2). Deactivation: MPTP N-oxygenation was efficiently mediated by FMOs in marmoset liver and brain microsomes. PTP formation was efficiently mediated by CYP2D6 in marmoset liver microsomes. FMOs, flavin-containing monooxygenases; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP^+, 1-methyl-4-phenylpyridinium; PTP, 4-phenyl-1,2,3,6-tetrahydropyridine; CYP, cytochrome P450.

circulating trimethylamine N-oxide (TMAO) levels (an independent risk factor for cardiovascular disease) and atherosclerosis.[4,5] *Fmo5*$^{-/-}$ mice exhibit a lean phenotype and are resistant to age-related changes in glucose homeostasis compared with wild-type mice, indicating that FMO5 is a regulator of metabolic aging.[58] *Fmo5*$^{-/-}$ mice also possess metabolic characteristics similar to those of germ-free mice, indicating that FMO5 is crucial for sensing or responding to gut bacteria.[59] However, conditional knockdown of brain FMOs has not been reported.

Further directions

The precise roles of FMOs in pathological processes remain to be determined. In-depth knowledge of FMO gene expression and protein localization and identification of substrates in the brain that are oxidized by FMOs may help in understanding the mechanisms of action of FMOs and their importance in the pathogenesis of neuronal degeneration and aging.

Conclusions

The potential involvement of FMOs in neurodegeneration and aging has been demonstrated in recent years. FMOs play important roles in metabolizing certain endogenous chemicals and xenobiotics in the brain, which participate in physiological and pathological processes. Knowledge of the expression and localization of FMOs in the brain, the endogenous chemicals and xenobiotics metabolized by FMOs, and the consequences of FMO deficiency can help us understand their involvement in neurodegeneration and aging.

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Conflict of interest

The authors declare no conflict of interests.

Author contributions

Writing of the original draft (BL); supervision (ZA).

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