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Review

The role of monoamine oxidase enzymes in the pathophysiology of neurological disorders

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ABSTRACT

Monoamine oxidase enzymes are responsible for the degredation of serotonin, dopamine, and norepinephrine in the central neurvous system. Although it has been nearly 100 years since they were first described, we are still learning about their role in the healthy brain and how they are altered in various disease states. The present review provides a survey of our current understanding of monoamine oxidases, with a focus on their contributions to neuropsychiatric, neurodevelopmental, and neurodegenerative disease. Important species differences in monoamine oxidase function and development in the brain are highlighted. Sex-specific monoamine oxidase regulatory mechanisms and their implications for various neurological disorders are also discussed. While our understanding of these critical enzymes has expanded over the last century, gaps exist in our understanding of sex and species differences and the roles monoamine oxidases may play in conditions often comorbid with neurological disorders.

1. Background

1.1. Discovery, function, and distribution in the brain throughout development and aging

In 1928, Mary Hare described an enzyme that catalyzed the oxidative deamination of tyramine, which she named tyramine oxidase (Hare, 1928). A decade later, the same enzyme was identified and given the name "monoamine oxidase" following the observation of its ability to catabolize adrenaline in liver, kidney, and small intestine cells (Blaschko et al., 1937; Pugh and Quastel, 1937). It was also localized in the brain, but its function in the central nervous system was uncertain at the time (Pugh and Quastel, 1937). Since then, we have learned that monoamine oxidases (MAOs) are mitochondrial outer membrane proteins that catalyze the degradation of various biogenic amines throughout the body. In the central nervous system, these include the neurotransmitters serotonin (5 H T), dopamine (DA), and norepinephrine (NE), as well as other trace amines (Youdim et al., 1988). Two isoforms exist in most vertebrates- monoamine amine oxidase-A (MAO-A) and monoamine oxidase-B (MAO-B)- which are encoded by distinct genes on the X chromosome. MAO-A is inhibited by clorgyline and preferentially degrades 5 H T, whereas MAO-B is inhibited by deprenyl and pargyline and preferentially degrades 2-phenylethylamine and benzylamine (Finberg and Youdim, 1983; Ochiai et al., 2006; Youdim et al., 1988). Both enzymes participate in the degradation of DA, NE, tryptamine, and tyramine in most species (Youdim et al., 2006; Garrick and Murphy, 1980; 1982).

Monoamines play a unique role in neural development. In addition to acting as neurotransmitters throughout prenatal life, they also contribute to neural differentiation and morphogenesis (Herlenius and Lagercrantz, 2001). MAOs are therefore positioned to indirectly impact morphological features of the brain and its neural circuitry. The cellular

Abbreviations: 5HT, serotonin; AD, Alzheimer's Disease; APP, amyloid beta precursor protein; AR, androgen receptor; ASD, Autism Spectrum Disorder; Aβ, amyloid beta; DA, dopamine; ER, estrogen receptor; FXS, Fragile-X Syndrome; KLF11, Kruppel like factor 11; MAO, monoamine oxidase; MAO-A, monoamine oxidase-A enzyme; *MAOA*, monoamine oxidase-A gene; *MAOA-VNTR*, *MAOA* linked polymorphic region; MAO-B, monoamine oxidase-B enzyme; *MAOB*, monoamine oxidase-B gene; MAOBI, monoamine oxidase-B inhibitor; MAOI, monoamine oxidase inhibitor; *MBin13*, *MAOB* rs1799836 intron 13 SNP; MDD, Major Depressive Disorder; MSA, Multiple Systems Atrophy; NE, norepinephrine; PD, Parkinson's Disease; PDD, Postpartum Depression; PSP, Progressive Supranuclear Palsy; R1, cell division cycle-associated 7-like protein; SNP, single nucleotide polymorphism; SNRI, selective norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitor; VNTR, variable number of tandem repeats; XCI, X-chromosome inactivation.

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localization of MAOs in the brain is similar among mammalian species. In humans, monkeys, cats, mice, and rats (Saura et al., 1992; Westlund et al., 1985; Kitahama et al., 1994) MAO-A is located predominately in catecholaminergic neurons, whereas MAO-B is predominately found in serotonergic neurons, histaminergic neurons, and astrocytes. MAOs do, however, display species differences in substrate metabolism. In rats, striatal DA is predominately catabolized by MAO-A, while in humans and vervet monkeys it is primarily catabolized by MAO-B (Garrick and Murphey, 1980; Watchel and Abercrombie, 1994).

The developmental trajectory of MAOs in the human and mouse brain is depicted in Fig. 1. Beginning in early fetal development, MAO-A activity predominates and reaches adult levels shortly after birth, whereas MAO-B activity is significantly lower at birth in both humans and rodents (Rao et al., 1995; Jourdikian et al., 1975; Melamed et al., 1990; Nicotra et al., 2004; Tong et al., 2013). In humans, MAO-B increases substantially during postnatal development and with age, while MAO-A appears to remain stable throughout life in healthy brains (Kornhuber et al., 1989). A similar pattern is observed in rodents, (Arai and Kinemuchi, 1988; Benedetti and Keane, 1980; Mantle et al., 1976; Koide and Kobayashi, 1984; Saura et al., 1994), however the magnitude of the MAO-B increase with age appears to be greater in humans, as the *ratio* of isoform B-to-A (B:A) shows species differences (see Fig. 1). In nonhuman primates and humans, the B:A ratio is significantly higher across the brain by adulthood (Saura et al., 1996; Garrick and Murphy, 1980; Tong et al., 2013).

Tong et al. (2013) conducted a survey of regional MAO distribution in healthy human brains, spanning 38 regions. The expression of MAOs was heterogenous, though both isoforms were most highly expressed in the hypothalamus, nucleus basalis, and the hippocampal uncus. Across all brain regions examined, MAO-B was significantly more abundant, with the B:A ratio ranging from 2.6 in the occipital cortex to 17.8 in the caudal corpus callosum (Tong et al., 2013). This study revealed three developmental phases for MAOs in the frontal cortex of healthy human brains. These included an infant phase (up to 1 year), a toddler phase (1–4 years), and the years thereafter. At birth, MAO-A levels were 78 % of adult levels and increased 50 % above adult levels by 7 months, after which levels declined and stabilized (see Fig. 1). MAO-B was barely detectable at birth but increased significantly over the first two years of life. From 18 years of age and up, MAO-B increased ~20 % per decade, whilst MAO-A remained stable. Using autoradiography, Saura et al. (1997) also observed a significant increase in MAO-B with age across 18 brain structures. In contrast to the steady increase in MAO-B that was observed by Tong et al. (2013), their data showed that MAO-B began to increase between ages 50–60 (see Fig. 1).

1.2. Genetic structure and polymorphisms

The *MAOA* and *MAOB* genes are located on the X-chromosome in mammals. Both genes are highly conserved, as humans, rats, and bovine share ~87 % *MAOA* sequence identity and ~88 % *MAOB* sequence identity (Grimsby et al., 1991). In humans, *MAOA* and *MAOB* genes are located near the Xp11.3 region of the X-chromosome, separated by about 50 kilobases and oriented in a tail-to-tail (3′-3′) manner (Lan et al., 1989) (Fig. 2). The two genes share ~70 % sequence identity and possess identical exon-intron organization, each with 15 exons and 14 introns (Chen et al., 1992). Their promoter regions share ~60 % sequence identity, are CG-rich, and contain multiple SP1 binding sites (Zhu et al., 1992). These characteristics suggest the two genes are derived from a common ancestral gene and may be the product of a gene duplication event (Grimsby et al., 1991). The lack of corresponding transcription factor binding sites in their promoters, however, suggests divergent regulatory mechanisms (Zhu et al., 1992). Such differences in regulation are the basis for their different developmental trajectories and distributions among tissue and cell types.

Several genetic polymorphisms that impact transcriptional efficiency have been identified in humans. The most widely studied *MAOA*

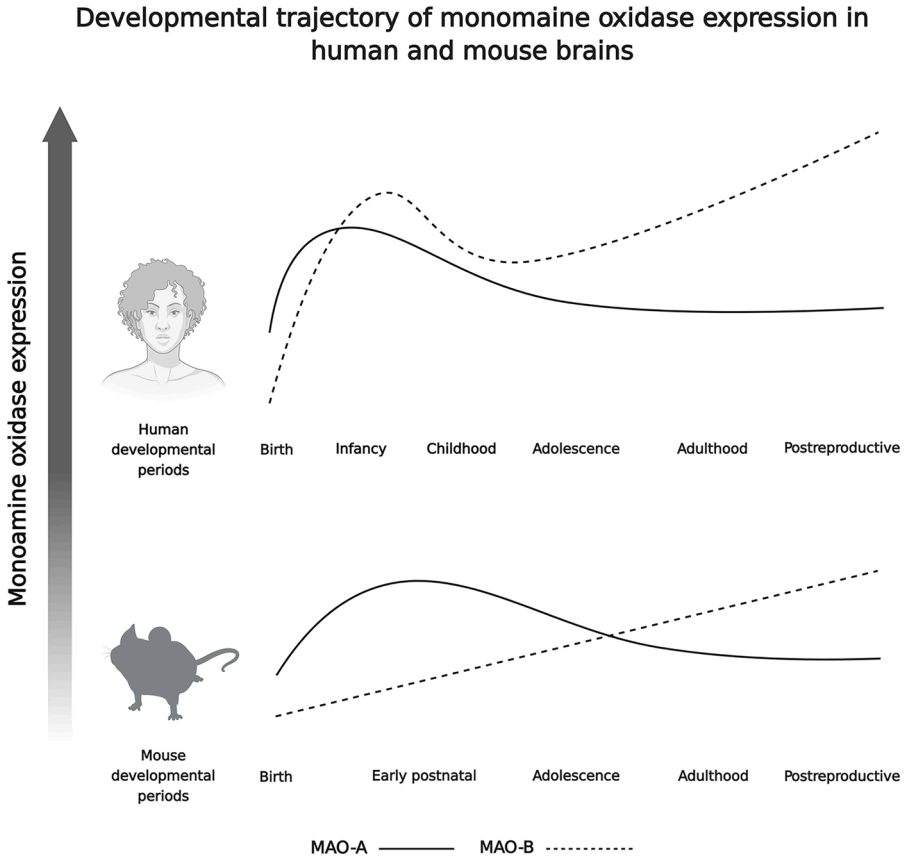

Fig. 1. In humans and mice, MAO-A is more abundant than MAO-B in the brain at birth. In humans, MAO-A expression peaks within the first year of life and then declines to reach adult levels, remaining stable thereafter. Comparatively, MAO-A is most highly expressed in mice during the early postnatal period, after which it also decreases and remains stable throughout life. In both species, MAO-B expression is low at birth and increases significantly with age. In humans, MAO-B expression increases rapidly during the first year of life, decreases slightly during childhood, and then increases steadily from adolescence to postreproductive life. In mice, MAO-B also increase with age, however this increase in less rapid. Developmental periods for mice were obtained from Brust et al. (2015) and MAO expression patterns were synthesized from studies on monoamine development in mice and humans (Melamed et al., 1990; Saura et al., 1994; Nicotra et al., 2004; Tong et al., 2013).

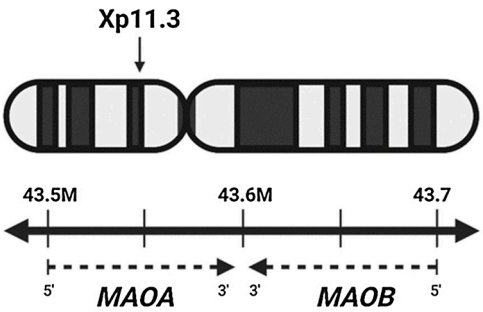

Fig. 2. In humans, *MAOA* and *MAOB* are oriented in a tail-to tail manner on the short arm of the X-chromosome at region Xp.11.3.

polymorphism was identified by Sabol et al. (1998) and is characterized by a 30-base pair variable number of tandem repeats (VNTR) located in the promoter region, approximately 1,000 base pairs upstream of the transcription start site. In the literature, this polymorphism is referred to as either *MAOA-VNTR* or *MAOA-LPR*, however, it will be referred to as *MAOA-VNTR* throughout this review. 3-, 3.5-, 4-, and 5-repeat *MAOA-VNTR* alleles have been observed, of which, the 3.5- and 4-repeat alleles result in significantly greater transcriptional activity relative to the 3- and 5-repeat alleles in *in vitro*. Although most *in vitro* studies have confirmed differential transcriptional activity, it is less clear whether *in vivo MAOA-VNTR* genotype is associated with enzyme activity (Shumay et al., 2012; Balciuniene et al., 2002; Schlüter et al., 2016). Despite this discrepancy, the *MAOA-VNTR* polymorphism has been shown to interact with childhood maltreatment and impact the incidence of mental health problems later in life (Caspi et al., 2002; Kim-Cohen et al., 2006) in addition to being associated with various neurological disorders (*e.g.*, Chang et al., 2019; Liu et al., 2015).

The *MAOB* intron 13 single nucleotide polymorphism (SNP), referred to as *MAOB rs1799836*, is located 36 bp upstream of the exon 14 start site (Kurth et al., 1993). Throughout this review, it will be referred to as the *MBin13* SNP. Two *MBin13* alleles exist, the "A" allele and "G" allele, which influence transcriptional activity in a tissue specific manner. While the A allele was associated with significantly higher transcriptional activity compared to the G allele in platelets (Garpenstrand et al., 2000), the opposite has been reported in the brain (Balciuniene et al., 2002; Löhle et al., 2018; Kakinuma et al., 2020). Because this review focuses on the role of MAOs in the brain, the *MBin13* A allele will be referred to as high-activity and the G allele as low-activity. This SNP has been associated with risk and disease features of Parkinson's Disease (PD) (Jakubauskiene et al., 2012; Zhang et al., 2016; Löhle et al., 2018; Kakinuma et al., 2020) and there is some evidence that it may interact with *MAOA-VNTR* geontype to impact transcriptional activity (Balciuniene et al., 2002). The mechanism underlying the ability of *MBin13* alleles to affect enzyme activity was investigated by Jakubauskiene et al. (2012), revealing a connection between the high-activity A allele and more efficient intron 13 splicing. The authors suggest that since splicing events vary in the rate at which they occur, the A allele's relatively increased efficacy at recruiting splicing factors may underlie its high-activity.

1.3. Sex differences in MAO regulation

Some of the most highly prevalent neurological disorders affect men and women disproportionately, not only in incidence, but also in symptomatology and disease course. For instance, women are two-times more likely to be diagnosed with Major Depressive Disorder (MDD) during their lifetime (Albert, 2015). Additionally, men diagnosed with MDD experience symptoms of anger, substance abuse, and risk-taking behavior more often than women (Martin et al., 2013). Autism Spectrum Disorder (ASD) has been reported to be more prevalent in males, however, female-specific presentations of ASD are sometimes overlooked and may contribute to this disparity (Rynkiewicz et al., 2016). Sex differences in neurodegenerative diseases have also been reported, with Alzheimer's Disease (AD) disproportionately affecting women (Viña and Lloret, 2010) and PD affecting more men (Miller and Cronin-Golomb, 2010).

Abnormal MAO activity and functional polymorphisms have been associated with neural and behavioral features of MDD, ASD, and neurodegenerative disease, with sex often mediating these associations. For example, in patients with MDD, *MAOA-VNTR* high-activity alleles were associated with slower treatment responses in women, but not men (Domschke et al., 2008). With implications for stress related mental illness, sex has also been found to mediate the association between *MAOA-VNTR* genotype and amygdala, hippocampus, and anterior cingulate cortex activity among adolescents with a history of childhood stress (Holz et al., 2016). Additionally, a novel *MAOB* haplotype was identified as being specific to females with ASD (Chakraborti et al., 2016). Differential regulation by sex hormones and proteins involved in sex determination may partially explain the observed sex differences in MAO function, as outlined below.

Estrogens regulate MAOs through canonical and non-canonical pathways (*e.g.*, Zhang et al., 2006) and operate in a tissue specific manner in rats and macaques (Chevillard et al., 1981; Holschneider et al., 1998; Gundlah et al., 2002). Estrogen targets genes in the canonical pathway that begins at the cellular membrane when estrogen binds to estrogen receptors (ERs), a class of nuclear receptor that includes two genetically and functionally distinct subtypes, ERα and ERβ. After estrogen binds, ERs translocate to the nucleus and regulate transcription by binding to estrogen response elements (EREs) located in regulatory regions of target genes. Alternatively, ERs can regulate target genes through transcriptional crosstalk, a non-canonical pathway which requires association with other transcription factors to exert their regulatory effects in the absence of EREs (Göttlicher et al., 1998; Safe, 2001).

A third non-genomic rapid signaling pathway is initiated when estrogen binds to the G-protein coupled receptor GPER1. Estrogen regulates neuronal activity by increasing intracellular calcium through this pathway (Brailoiu et al., 2007; Funakoshi et al., 2006). GPER1 is located on the plasma membrane, endoplasmic reticulum, and Golgi apparatus in neurons (Waters et al., 2015) and is widely distributed in the brains of rats (Brailoiu et al., 2007), mice (Hazell et al., 2009), and humans (Owman et al., 1996). In rodent studies, estrogen signaling through GPER1 contributed to spatial memory (Hammond et al., 2012), social memory (Ervin et al., 2015), novelty recognition (Gabor et al., 2015), and dendritic spine remodeling (Akama et al., 2013; Gabor et al., 2015). Importantly, this signaling pathway has been implicated in PD (Bourque et al., 2013) and schizophrenia (Macêdo et al., 2020), which are both also associated with monoamine dysregulation (Takano, 2018; Tong et al., 2017).

Evidence from macaque (Gundlah et al., 2002; Smith et al., 2004) and rat studies (Chevillard et al., 1981) demonstrate that estrogen negatively regulates *MAOA*. Estrogen has been found to improve mood in perimenopausal women with depressive disorders (Cohen et al., 2003; Soares et al., 2001), potentially through negative regulation of *MAOA*. PET imaging has revealed that MAO-A levels are elevated in patients with MDD (Meyer et al., 2006). Although *MAOA* lacks EREs, it possesses SP1 binding sites in its regulatory region, making it possible that estrogen exerts its regulatory effects through crosstalk with SP1 (Safe, 2001). *MAOB* contains several ERE half-sites in its regulatory region that enable ERs to act as negative regulators *in vitro* (Zhang et al., 2006). Additionally, estrogen-related receptors positively regulate *MAOB* and compete with ERs for binding in the promoter region *in vitro* (Zhang et al., 2006).

Androgens exert their effects through androgen receptors (ARs), which are also a type of nuclear receptor, to regulate MAOs through canonical and non-canonical pathways (Ou et al., 2006). *MAOA* contains an androgen/glucocorticoid response element in its regulatory region

(Haelens et al., 2001) and ARs also interact with SP1 to regulate *MAOA* (Ou et al., 2006). Since testosterone is converted to estrogen by aromatase, it may also indirectly regulate MAOs through ER signaling (Vrtačnik et al., 2014). Another important transcriptional activator that acts on *MAOA* is testis-determining factor, which is encoded by the Y-chromosome gene *SRY* (Wu et al., 2009). Both *MAOA* (Tong et al., 2017) and *SRY* (Lee et al., 2019) expression abnormalities are implicated in PD, a neurodegenerative disease that is more prevalent among men (Baldereschi et al., 2000; Van der Eeden et al., 2003).

Less is known about the influence of androgens on *MAOB* regulation. An *in-situ* hybridization study of the dorsal raphe in gonadectomized Japanese macaques found an increase in MAO-B expression in response to testosterone replacement accompanied by aromatase inhibition (Bethea et al., 2015). The mechanism underlying testosterone's ability to regulate *MAOB* is not clear, as androgen response elements have not been observed in the regulatory region of *MAOB*, however, yet-to-be-discovered noncanonical regulatory mechanisms are possible avenues.

2. The significance of MAOs in neurological disorders

MAOs were recognized for their role in mood and behavior regulation in the 1950s. Clinical studies investigating the efficacy of the monoamine oxidase inhibitor (MAOI) iproniazid in tuberculosis patients revealed that individuals who were administered the drug became more active and social (Selikoff et al., 1952). The stimulating effect of iproniazid was initially considered a mere side-effect, and its use as a treatment for depression was quickly pursued. Subsequent studies demonstrated its effectiveness (Crane, 1957; Loomer et al., 1957) and led to the development of additional MAOIs to treat depression (Maass and Nimmo, 1959; Tedeschi et al., 1959; Robinson et al., 1973). MAOIs are no longer widely prescribed today due to adverse side effects and drug interactions, however, they are considered second-choice options for treatment of resistant and atypical depression (López-Munoz et al., 2007; Menkes et al., 2016).

Early genetic studies also highlighted the role of MAOs in behavior and cognition. Initially, learning deficits and psychoses were observed in a subset of patients with Norrie Disease, a developmental disorder that affects the eyes and occurs disproportionately in males (Warburg, 1968; Sims et al., 1989). Norrie Disease is caused by a mutation in the *NDP* gene, which is arranged in tandem with *MAOA* and *MAOB* on the X-chromosome (Berger, 1998). In some patients, the MAO genes are also affected, as evidenced by lack of MAO-A mRNA in fibroblasts, lack of MAO-B activity in platelets, and elevated monoamine levels in plasma and urine (Lenders et al., 1996). Additionally, Brunner et al. (1993) discovered that the manifestation of a severe behavioral syndrome among males in a Dutch family, which was characterized by violent behavior and impulsive aggression, was due to a loss-of-function mutation in the *MAOA* gene (Brunner et al., 1993). A decade later, the *MAOA-VNTR* polymorphism was found to interact with childhood adversity to impact antisocial behavior in adulthood (Caspi et al., 2002).

Not only do MAO substrates cooperatively mediate a wide range of behaviors and cognitive processes, including aggression (Yanowitch and Coccaro, 2011), motivation (Lammel et al., 2014), and movement (Yin, 2014), their metabolites and molecular byproducts also have substantial effects on a wide range of neural functions. Substrate oxidation by both MAOs produces hydrogen peroxide and ammonia, which are implicated in the pathophysiology of various neurological disorders (Cohen et al., 1997; Okusaga, 2014). MAOs are also crucial to the formation and function of neurotoxins. MAO-B mediates the conversion of 1-methyl-4--phenyl-1,2,3,6-tetrahydropyridine (MPTP) to its neurotoxic metabolite 1-methyl-4-phenylpyridinium, which is known to induce PD symptoms and pathology (Sian et al., 1999; Heikkila et al., 1984). This exogenous neurotoxin was accidentally identified when four people presented at a hospital displaying PD-like symptoms after injecting this compound into their bloodstream intravenously under the impression that it was synthetic heroin (Langston et al., 1983). MPTP has since been utilized to create animal models of PD (*e.g.*, Duty and Jenner, 2011). As for endogenous neurotoxins, MAO-A, but not MAO-B, was observed to bind N-methyl(R)salsolinol to induce apoptosis in neuroblastoma SH-SY5Y cells (Yi et al., 2006).

Given their multifaceted role in neural function and brain health, MAOs have been pursued as therapeutic targets for decades. Synthetic and natural MAOIs show great promise for their neuroprotective and neurorestorative effects (*e.g.*, Kong et al., 2015; Weinreb et al., 2008; Dhiman et al., 2019), their efficacy for treating mood disorders (Menkes et al., 2016), and for alleviating symptoms and slowing disease progression in neurodegenerative disease (Riederer and Laux, 2011). In the following sections, the role of MAOs in psychiatric, neurodevelopmental, and neurodegenerative disease will be discussed, with a focus on human studies.

2.1. MAOs in depressive disorders

The earliest attempts to explain the etiology of depression focused on monoamine signaling in the brain (Hindmarch, 2001). The monoamine hypothesis of depression postulates that depression is a result of monoamine deficiency, and therefore increasing CNS monoamine availability through pharmacological agents should lead to remission. This hypothesis is partially supported, as antidepressants that increase monoamine availability, namely MAOIs, selective serotonin reuptake inhibitors (SSRIs), and selective norepinephrine reuptake inhibitors (SNRIs), are effective in approximately 60–70 % of patients (Santarsieri and Schwartz, 2015). Like its clinical presentation, the pathophysiology of depression is heterogenous and complex, contributing to the unsurprising fact that some patients do not respond to antidepressant therapy. Neuroimaging studies revealed that even among patients diagnosed with the same subtype of depression, the underlying neural findings can differ significantly. Using fMRI, Drysdale et al. (2017) reported four neurophysiological "biotypes" among patients with MDD, which were each characterized by distinct resting state features in limbic and frontostriatal networks.

Of the two MAOs, MAO-A appears to be more involved in the pathophysiology of depression, as elevated MAO-A activity and expression have consistently been observed in humans diagnosed with depressive disorders and in animal models of depression (Meyer et al., 2006; Zhen et al., 2017; Schulze et al., 2000; Hampp et al., 2008). This observation may be explained, in part, by stress-induced upregulation of *MAOA* (Ou et al., 2006). *MAOA* is a pro-apoptotic gene (De Zutter and Davis, 2001), therefore its increased expression may also play a role in long-term stress-induced neuronal cell death (Lee et al., 2002; Meyer, 2017). Contributing to this cascade, Kruppel like factor 11 (KLF11) is produced in response to neuronal stress and enhances the expression and enzymatic activity of MAO-A (Grunewald et al., 2012). In a postmortem study, KLF11 and MAO-A protein levels were significantly higher in patients with MDD (Harris et al., 2015). Conversely, cell division cycle-associated 7-like protein (R1) is a repressor of MAO-A, and its expression in the prefrontal cortex of patients with MDD is significantly lower compared to healthy controls (Johnson et al., 2011). Such findings highlight the diverse mechanisms by which stress directly and indirectly contributes to dysfunctional monoaminergic signaling in depression. The regulation of MAO-B in mental illness is not well-defined. Even so, MAO-B is also positively regulated by glucocorticoids and KLF11 and negatively regulated by R1 (Chen et al., 2011; Ou et al., 2004). Interestingly, a PET imaging study revealed that MAO-B distribution volume, which is a proxy for density, was significantly higher in patients with major depressive episodes (Moriguchi et al., 2019), a finding that calls attention to the need for further investigation of MAO-B's involvement the pathophysiology of depression and other stress-related psychiatric disorders.

In a Chinese population study of 230 patients with MDD and 217 healthy controls, Yu et al. (2005) found the 4-repeat "high-activity"

MAOA-VNTR allele to be over-represented in males and females, even when controlling for X-inactivation in females. This finding agrees with some studies (Schulze et al., 2000), but not others (Kunugi et al., 1999; Syagailo et al., 2001). Female carriers of the high-activity *MAOA-VNTR* allele were reported to have a significantly worse response to 4-week SSRI treatment compared to those who were homozygous for the 3-repeat "low-activity" allele. Though less is known about the role of MAO-B in depressive disorders, *MAOB* variants may also impact treatment response, as *MBin13* genotype has been associated with treatment response to SSRIs and SNRIs in female patients (Tadić et al., 2007).

MAOA-VNTR genotype may also impact connectivity patterns in the brain. A fMRI study conducted by Dannlowski et al. (2009) found that MDD patients who were high-activity carriers exhibited significantly reduced amygdala-prefrontal cortex connectivity compared to controls. Furthermore, MDD carriers of the high-activity allele showed the weakest connectivity of all subgroups investigated. This reduced connectivity predicted more than 40 % of the variance in clinical variables associated with a longer and more severe course of the disorder, particularly among women (Dannlowski et al., 2009). This finding may help explain the reduced response to antidepressant therapy in female carriers of the high-activity *MAOA-VNTR* allele (Domschke et al., 2008; Yu et al., 2005).

Abnormal MAO activity also contributes to peripartum and postpartum depression (PPD). MAO-A levels peak in women approximately 5 days after giving birth and this peak is associated with a period known as "postpartum blues", which commonly includes mood changes, anxiety, and difficulty sleeping (Sacher et al., 2010). This period is sometimes a prodromal state for PPD, as it may become more persistent and severe. One study aimed to counter the effects of the postpartum MAO-A peak with a dietary supplement containing monoamine precursor amino acids and antioxidants and reported this treatment to be effective at diminishing vulnerability for depressed mood during this high-risk time (Dowlati et al., 2017).

Elevated MAO has been observed in the brains of women with PPD and in undiagnosed women who display some symtoms. A PET study revealed that women with PPD and those who had a predisposition for postpartum crying exhibited elevated MAO-A density in the prefrontal and anterior cingulate cortex (Sacher et al., 2015). These two regions are heavily involved in the pathogenesis of depression, as they function as both executive and affective processing centers (Elliott et al., 2002; Koenigs and Grafman, 2009; George et al., 1997). Research also suggests that the effects of maternal depression may reach beyond the mother, as prenatal maternal depression severity was negatively correlated with MAO-A expression in the placenta (Blakeley et al., 2013). This observation may partially underlie the association between maternal depression and altered neuropsychological outcomes in their children (Koutra et al., 2017; Duan et al., 2019). Further research is needed to clarify the relationship between placental MAO-A and child development; however, one study suggests placental MAO-A may interact with maternal stress to impact aspects of infant temperament (Pehme et al., 2018).

2.2. MAOs in schizophrenia

Schizophrenia is a chronic psychiatric disorder that is characterized by positive symptoms, which often present as hallucinations, paranoia, and distorted perceptions of reality, and negative symptoms, which often present as blunted affect, avolition, and attentional impairment (Smigielski et al., 2020). The etiology of schizophrenia is unclear, however hypotheses have focused on neurodevelopment (Negrón-Oyarzo et al., 2016), neurodegeneration (Pérez-Neri et al., 2006), genetics (Gejman et al., 2010), and neurotransmission (Howes et al., 2015). The dopamine hypothesis of schizophrenia, which posits that abnormal dopaminergic signaling is an underlying feature of the disorder, was first put forth in the 1970s after antipsychotic drugs were found to exert their therapeutic effects through dopamine receptor signaling (Seeman and Lee, 1975; Seeman et al., 1976; Creese et al., 1976; Snyder, 1976). Over the past several decades, the dopamine hypothesis has been refined to include regional specificity of dopamine signaling abnormalities (Davis et al., 1991). In some cases, striatal hyperdopaminergia and frontal cortical hypodopaminergia have been observed, the former being associated with positive symptoms and the latter with negative symptoms and cognitive dysfunction (Meyer-Lindenburg et al., 2002; Howes and Kapur, 2009).

In a postmortem study, Purves-Tyson et al. (2017) investigated the molecular basis of dopamine dysregulation by measuring expression levels of 12 dopamine-related proteins, including MAO-A and MAO-B, in the human midbrain. MAO-A mRNA levels were 45 % higher in schizophrenia patients compared to controls. MAO-B and catechol-O-methyl transferase mRNA showed no difference, the latter being an enzyme that also catabolizes intracellular DA in human glia (Kastner et al., 1994). The authors suggested that this observation may reflect a compensatory mechanism meant to balance extracellular DA. Alternatively, elevated midbrain MAO-A may contribute to increased 5 H T breakdown, and consequently, reduced inhibition of DA firing. The observation of elevated MAO-A in the midbrain suggests dysfunctional transcriptional regulation of *MAOA* may occur in certain brain regions and contribute to aspects of schizophrenia pathophysiology.

Schizophrenia is a polygenic disorder, as an amalgam of common and uncommon genetic variants appear to contribute to disease risk (Henriksen et al., 2017). MAO gene variants have been associated with schizophrenia and its relevant symptoms, however, results from many studies are inconsistent. Jönsson et al. (2003) tested for associations between *MAOA-VNTR* alleles and schizophrenia in 133 patients and 377 control subjects and found an association between the low-activity *MAOA-VNTR* allele and schizophrenia that was only present in men. The opposite has been reported in similar association studies (Syagailo et al., 2001; Li and He, 2008). Several exonic *MAOA* SNPs have also been associated with affective disturbances among Korean males with schizophrenia (Kim et al., 2014). Importantly, the SNPs identified in that study had previously been shown to have functional effects on transcriptional efficiency (Hotamisligil and Breakefield, 1991) and social behavior (Li et al., 2007). Several studies have also revealed an association between *MAOB* genetic variants and susceptibility for schizophrenia (Carrera et al., 2009; Wei et al., 2011), however other studies failed to find concordance (Coron et al., 1996; Matsumoto et al., 2004). Taken together, while there are interesting lines of evidence, there appears to be no clear association between MAO gene variants and schizophrenia disease risk or symptom severity.

Epigenetic factors are thought to play a moderate role in the etiology of schizophrenia (Smigielski et al., 2020). Several studies have found a relationship between certain epigenetic markers and schizophrenia. For example, blood cells showed abnormal methylation at certain CpG sites within the *MAOA* promoter among males with schizophrenia (Chen et al., 2012). Another study observed increased methylation of the *MAOA* and *MAOB* promoter in the prefrontal cortex of affected females (Yang et al., 2012). The possibility that abnormal epigenetic regulation of *MAOA* may play a more prominent role than *MAOA-VNTR* genotype in schizophrenia is supported by the observation that genotype did not predict *in vivo* enzymatic activity in healthy male subjects, however a strong association between site-specific methylation within the core promoter region and MAO-A levels was observed (Shumay et al., 2012).

2.3. MAOs in neurodevelopmental disorders

ASD is a diagnosis that encompasses several prevalent neurodevelopmental disorders. These include Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified. The features and severity of ASD vary widely, however, individuals commonly possess social interaction impairments, verbal and nonverbal communication challenges, ritualized patterns of behavior, and hypo- or hyperreactivity to sensory input (Constantino and Charman,

2016). The etiology of ASD is complex, and genetic and environmental factors are thought to play a role (Amaral, 2017). Approximately 100 genes have been found to confer ASD risk, one being the X chromosome gene *FMR1* (De Rubeis et al., 2014; Geschwind and State, 2015). A mutation in the *FMR1* gene is the cause of Fragile X Syndrome (FXS) (Verkerk et al., 1991), which is characterized by developmental delays, learning disabilities, and social and behavioral problems. 60 % of individuals with FXS also meet the diagnostic criteria for ASD (Harris et al., 2008). Among individuals diagnosed with FXS, ASD, and those diagnosed with both, MAO gene variants have been associated with brain structure (Wassink et al., 2014), behavior (Cohen et al., 2011), and treatment response (AlOlaby et al., 2017).

Despite the social and behavioral similarities observed in ASD and FXS, various structural differences have been observed in the brain (Hoeft et al., 2011; Meguid et al., 2010; Hazlett et al., 2009). Nevertheless, *MAOA-VNTR* genotype appears to similarly impact brain structure among males diagnosed with either or both disorders. Wassink et al. (2014) found that, in both conditions, the low-activity *MAOA-VNTR* allele was associated with increased gray and white matter in all cerebral lobes, with the strongest association observed in the frontal lobes (Wassink et al., 2014). While the low-activity allele has been associated with more severe sensory behaviors, arousal regulation problems, aggression, and social communication problems among males with ASD (Cohen et al., 2011), *MAOA-VNTR* genotype has not been associated with behaviors or symptom severity in FXS (Crawford et al., 2021; Hessl et al., 2008). One study that examined males with FXS found that carriers of the high-activity *MAOA-VNTR* allele were more likely to be on SSRI and SNRI medication (Hessl et al., 2008). Interestingly, individuals with FXS who carry the high-activity allele have also been found to have a worse treatment response to sertraline, an SSRI (AlOlaby et al., 2017).

Individual and maternal *MAOA-VNTR* genotype also contributes to ASD risk in males (Salem et al., 2013). Males hemizygous for the high-activity allele were two times more likely to be diagnosed with ASD compared to those hemizygous for the low-activity allele (Tassone et al., 2011). Additionally, mothers who were homozygous for the high-activity allele had a significantly higher risk of having a son with ASD, even after adjusting for maternal age and ethnicity (Tassone et al., 2011). Mothers homozygous for the high-activity allele were also more likely to have sons who displayed more aggression, fear, and ritualistic behaviors (Cohen et al., 2011). However, the high-activity allele may not contribute to risk in all populations, as one meta-analysis suggests that it is associated with ASD among white American and European males, but not in Egyptian, West Bengal, and Korean populations (Kisková and Gabriková, 2015).

Less is known about the role of MAO-B in ASD etiology, although mouse models suggest that it also may contribute to ASD pathophysiology and associated behaviors (Bortolato et al., 2013). Perfilyeva et al. (2019) failed to find an association between *MBin13* genotype and ASD in a Kazakhstani population. Similarly, no relationship between *MBin13* genotype and ASD was reported in a study of male Croatian children (Nikolac Perkovic et al., 2014). However, an association between the low-activity G allele and ASD was detected in both sexes in an Egyptian population (Salem et al., 2013). Interestingly, though Perfilyeva et al. (2019) found no association between ASD and *MBin13* genotype, they did find that female carriers of the A allele were more likely to have more severe ASD cases. In a comprehensive *MAOB* SNP and haplotype association study, Chakraborti et al. (2016) found that the A allele was associated with significantly elevated platelet 5 H T among males. That same study also identified three haplotypes that were associated with ASD, one of which was specific to females (Chakraborti et al., 2016). These results suggest that *MAOB* gene variants may play a role in etiological sex differences observed in ASD. This possibility is particularly intriguing given the observation that the *MAOB* genomic region may escape X-chromosome inactivation in females and impact social cognition (Good et al., 2003).

Dramatic changes occur in the serotonergic system from birth to adulthood, the patterns of which have been found to differ in those with ASD compared to control subjects (Muller et al., 2016). In ASD, low capacity for 5 H T synthesis in the brain (Chugani et al., 1999) and elevated whole blood 5 H T (Schain and Freedman, 1961) has been consistently observed. 5 H T is largely contained to platelets in the blood (Anderson et al., 1987), and serum hyperserotonemia is observed in ~30 % of ASD cases (Gabriele et al., 2014). MAO-B is expressed in platelets and has therefore been investigated for its role in ASD and hyperserotonemia with mixed results. Some studies have reported no association between MAO-B platelet activity and ASD (Boullin et al., 1975; Takahashi et al., 1977; Launay et al., 1988). In contrast, Hranilović et al. (2009) measured MAO-B activity in the platelets of postpubertal males and females with ASD. Their sample included a subset of individuals that did not display hyperserotonemia and another that did. Overall, MAO-B activity was significantly higher in both males and females with ASD compared to controls. Additionally, individuals with ASD who displayed hyperserotonemia showed significantly greater MAO-B activity compared to the non-hyperserotonemia ASD group (Hranilović et al., 2009).

MAO-A activity levels have also been linked to the abnormal serotonergic system features in ASD. Gu et al. (2017) observed ~30 % decrease in MAO-A activity in the cerebellum of children aged 4–12 with ASD compared to control subjects, with no differences in MAO-B activity (Gu et al., 2017). Interestingly, Chugani et al. (1997) observed a unilateral decrease in 5 H T synthesis capacity in the frontal cortex and thalamus of boys with ASD, which was restricted to the left hemisphere in five of the seven subjects studied. This decrease was associated with an increase in the contralateral dentate nucleus of the cerebellum (Chugani et al., 1997). Together, these findings suggest an inverse relationship between 5 H T synthesis and MAO-A activity in the cerebellum in ASD, which may affect signaling to distant brain regions, including the frontal cortex. Astrogliosis in the cerebellum and frontal cortex in addition to Purkinje cell loss have been observed in ASD, further implicating these two regions in ASD pathology (Courchesne and Pierce, 2005; Vargas et al., 2005).

2.4. MAOs in neurodegenerative disease

Neurodegenerative disease is a leading cause of disability in elderly populations (GBD, 2017). AD and PD are the most prevalent neurodegenerative diseases worldwide, affecting an estimated 24 million and 6.1 million people, respectively (Erkkinen et al., 2018; GBD, 2016; Reitz et al., 2011). PD is a heterogenous disease of genetic and sporadic origin that is characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta (Dickson, 2012). Loss of this neuronal population results in striatal DA denervation, leading to motor problems such as rigidity, bradykinesia, resting tremor, and postural instability. Hallmark motor symptoms are often what prompt diagnosis, however, sleep disturbances, depression, and cognitive impairment are often present for years prior to diagnosis (Goldman and Postuma, 2014). Another pathological feature that is often observed in, but not specific to, PD, are Lewy Bodies- intracellular neuronal aggregates that are made up of the protein α-synuclein (Grazia Spillantini et al., 1998; Schneider and Alcalay, 2017). Currently, the most common and effective treatment for PD is DA replacement, which is achieved through administration of Levadopa (l-dopa), a direct precursor of DA.

Birkmayer et al. (1975) conducted the first clinical trial for the use of the selective monoamine oxidase-B inhibitor (MAOBI) L-deprenyl, also known as selegiline, as an adjunctive therapy to Levodopa in PD and reported it to have a beneficial effect on symptoms. Subsequent studies demonstrated that patients who received selegiline in addition to Levodopa had a better survival rate compared to those treated with Levodopa alone, suggesting that selegiline worked as a disease modifying agent by slowing neurodegeneration (Birkmayer et al., 1985). Later, the selective MAOBI rasagiline was shown to enhance

extracellular DA levels in the striatum in monkeys (Finberg et al., 1998) and had greater neuroprotective effects than selegiline in neuronal cultures through activation of anti-apoptotic pathways (Youdim et al., 2005). In clinical studies, rasagiline treatment reduced functional decline in both the short- and long term (Blandini, 2005). These results suggest that inhibition of MAO-B in PD is effective because it increases extracellular DA in the striatum and aids in preventing cell death. MAOBIs continue to be used in the treatment of PD (Stocchi et al., 2015). Additional research on the effects of MAO inhibition in PD is warranted, particularly regarding its role in inflammatory signaling and astrocyte activation. MAO-B was recently shown to drive NLRP3 inflammasome activation (Sánchez-Rodríguez et al., 2020), which is known to play a crucial role in PD neural pathology (Yan et al., 2020). Additionally, elevated MAO-B in astrocytes was observed to induce PD-like pathology in a mouse model (Mallajosyula et al., 2008).

Using quantitative immunoblotting, Tong et al. (2017) measured MAO-A and MAO-B protein concentration in postmortem brains from individuals diagnosed with PD, multiple systems atrophy (MSA), and progressive supranuclear palsy (PSP). MSA and PSP are considered "Parkinson's-plus" disorders due to their similarities with PD in addition to more widespread, unique pathological features (O'Sullivan et al., 2008). Tong et al. (2017) observed significantly elevated MAO-B expression in the putamen in MSA, in the substantia nigra, caudate, putamen, and frontal cortex in PSP, and in the frontal cortex in PD. MAO-A levels were significantly decreased in the putamen in MSA and significantly increased in the caudate in PSP and putamen in PD. Their findings demonstrate distinct MAO dysregulation patterns in three similar neurodegenerative diseases. An unexpected finding in this study was the observation that MAO-A was elevated in the putamen in PD. DA denervation of the striatum is a pathological feature of PD and MAO-A is thought to mainly be expressed in dopaminergic neurons (Westlund et al., 1985, 1988). The authors suggest the unexpected increase may be due to hyperexpression of MAO-A by the surviving dopaminergic neurons, which may function as a compensatory mechanism.

A meta-analysis of the *MBin13* SNP in PD revealed an association between the high-activity A allele and disease risk (Zhang et al., 2016). This study also found that history of smoking was a preventative factor in PD, irrespective of genotype (Zhang et al., 2016). PET imaging has shown that smokers possess significantly lower MAO-B activity in the brain compared to non-smokers (Fowler et al., 1996). This suggests that smoking may compound the impact low-activity *MBin13* G alleles have on DA level in the brain, while also compensating for the impact of high-activity *MBin13* A alleles. This observation raises the question of whether MAO-B inhibition may be used as a preventative treatment to decrease PD risk.

MAOs have also been implicated in AD, which is a complex neurodegenerative disease characterized by cognitive dysfunction, personality changes, and memory loss (Blennow et al., 2006). The most common type of AD is late-onset, accounting for ~95 % of all cases (Reitz and Mayeux, 2014). Pathologically, senile plaques formed by amyloid beta (Aβ) and neurofibrillary tangles composed of phosphorylated tau protein are observed, which contribute to neurodegeneration, particularly in the hippocampus and cortex (Mattson, 2004). The underlying disease mechanisms of AD remain uncertain, however numerous hypotheses have been put forth over the past several decades. The amyloid hypothesis for AD posits that Aβ precursor protein (APP) metabolism dysregulation and Aβ deposition are the core events that drive AD pathology (Hardy and Selkoe, 2002). With relevance to this hypothesis, MAO-B has been found to play a key role in Aβ formation. Using proximity ligation assay and immunoprecipitation, Schedin-Weiss et al. (2017) demonstrated that MAO-B is associated with γ-secretase in human and rat neurons. Additionally, siRNA silencing of *MAOB* in neuronal cultures significantly reduced intraneuronal Aβ42 production while overexpression of *MAOB* enhanced it. γ-secretase is involved in the proteolytic processing of APP, which is required to form Aβ peptides (Steiner et al., 2008). In addition to observing a functionally significant association between MAO-B and γ-secretase, the authors also reported more intense MAO-B immunohistochemical staining in the hippocampus, entorhinal cortex, and frontal cortex in the brains of AD patients compared to age matched controls, consistent with previous reports of elevated MAO-B activity in the AD brain (Adolfsson et al., 1980; Oreland and Gottfries, 1986). These findings highlight both MAO-B and γ-secretase as potential targets for reducing Aβ formation in AD.

While MAO-B expression and activity is increased in the brains of patients with AD, conflicting reports about changes to MAO-A activity exist. A radioenzymatic study observed significantly lower MAO-A activity in the frontal cortex of AD patients compared to controls (Kennedy et al., 2003). mRNA expression data, however, show significantly elevated MAO-A and MAO-B mRNA levels in the frontal cortex of AD patients (Emilsson et al., 2002). Currently, MAOBIs have not be shown to significantly improve the course of AD, however clinical trials have suggested some beneficial effects such as improved cognition with selegiline treatment (Finali et al., 1991) and less brain atrophy following treatment with the multitargeted MAOBI ladostigil (Schneider et al., 2019).

3. Future directions

Increased inflammation and dysregulated neuroendocrine signaling have been observed in depressive disorders (Lee and Giuliani et al., 2019; Woelfer et al., 2019; Milaneschi et al., 2020), schizophrenia (Khandaker et al., 2015), ASD (Onore et al., 2012), and neurodegenerative diseases (Guzman-Martinez et al., 2019). MAOs are known to promote inflammation through the production of reactive oxygen species (Gao et al., 2014), therefore further investigation of their involvement in inflammation and related immunometabolic processes may enhance our knowledge about the pathophysiology of multiple highly prevalent disorders. Among depressive disorders, inflammation appears to play a prominent role in the pathophysiology of atypical depression (Łojko and Rybakowski, 2017). This subtype of depression is characterized by earlier age of onset, longer, more severe, and recurrent episodes, and is often associated with obesity, cardiovascular disease, and metabolic syndrome (Brailean et al., 2020). Genomic studies show that atypical depression and immunometabolic traits share a genetic predisposition (Badini et al., 2020; Milaneschi et al., 2017). Additional knowledge about the role of MAOs in atypical depression may help clarify the mechanisms that underlie the early age of onset observed in this patient population. Furthermore, since MAOs also play a role in conditions comorbid with atypical depression (Deshwal et al., 2017; Sturza et al., 2019), elucidation of their involvement beyond neural pathophysiology may provide insight on therapeutic approaches that address multiple afflictions.

MAOA and *MAOB* are located on the X-chromosome and are assumed to be subjected to X-chromosome inactivation (XCI) in females. XCI is a mechanism that functions to compensate for the imbalance of X-chromosome genes between sexes. Based on studies in mice, random XCI begins during embryonic development and persists throughout adult life (Patrat et al., 2020). This means that in females, maternal and paternal alleles should be expressed at a ratio of 50:50 throughout life. Some evidence suggests MAO genes escape XCI in humans (Jansson et al., 2005; Harro et al., 2001; Carrel and Willard, 2005), a phenomenon that has been observed in other species (Carrel and Brown, 2017), and this may play an important role in neurodevelopment, social cognition, and emotional learning (Good et al., 2003). It may also help explain why women are predisposed to certain mood disorders, such as depression (Jansson et al., 2005). In support of these notions, Pinsonneault et al. (2006) investigated the effect of polymorphisms and epigenetic factors on *MAOA* expression in the female brain by comparing the expression of one *MAOA* allele against another in a single individual. They observed a wide range of allele ratios within their sample, which suggests that additional *cis*-acting factors likely contribute to dosage compensation in females as opposed to being solely the result of XCI. They also observed a

substantially greater degree of CpG methylation of the *MAOA* promoter in females compared to males (Pinsonneault et al., 2006). These findings highlight the complexity of *MAO* gene regulation in females, which remains poorly understood. Future studies that aim to elucidate sex differences in MAO gene regulation throughout development may provide insight into why risk, severity, and treatment response differs between males and females in various neural disorders.

Examination of species differences in MAO expression throughout the lifespan is another intriguing topic for future studies. The developmental trajectory of MAOs have been characterized in humans (Tong et al., 2013; Saura et al., 1997) and rodents (Saura et al., 1994), however little is known about this topic in non-human primate brains. Macaques, which are cercopithecoid monkeys that belong to the speciose and behaviorally diverse genus *Macaca*, may be particularly useful for clarifying the regulatory mechanisms that influence MAO expression and associated behaviors. Notably, macaques possess a homologous *MAOA-VNTR* polymorphism to that observed in humans, and it too has been found to interact with rearing environment to influence aggression (Newman et al., 2005). Additionally, species differences in *MAOA-VNTR* allele frequency have been observed in Japanese and rhesus macaques (Jones et al., 2020a), which may contribute to behavioral, neural, and serotonergic system differences that have been observed between the two species (Lee et al., 2018; Jones et al., 2020b). Macaques have also been found to display a naturally occurring depression that resembles the human mood disorder (Xu et al., 2015). In addition to genetic and behavioral similarities, humans and cercopithecoid monkeys possess a greater MAO-B:MAO-A ratio in the brain compared to rodents (Garrick and Murphy, 1980). Macaques also possess a life history that more closely reflects human developmental periods. Together, these features make the macaque a promising model for investigating the genetic and regulatory mechanisms that influence MAO expression and associated neuroanatomical features, behavior, and cognition throughout development, with implications for various neurological disorders.

4. Conclusion

Our understanding of the role MAOs play in neuropsychiatric, neurodevelopmental, and neurodegenerative disease has grown immensely since their discovery nearly 100 years ago. In depressive and neurodevelopmental disorders, functional MAO polymorphisms have consistently been implicated in etiology and pathophysiology, while in schizophrenia, functional polymorphisms contribute to disease features in a less apparent way and alternative regulatory mechanisms may play a more prominent role. New insights on the critical role MAOs play in neurodegenerative disease highlight their promise as therapeutic targets. Future directions that will enhance our knowledge of MAO biology in the context of neurological disorders should focus on inflammatory signaling, sex-specific regulatory mechanisms, and nonhuman primate comprative research.

Declaration of Competing Interest

The authors report no declarations of interest.

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