Review

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Monoamine oxidases in major depressive disorder and alcoholism

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ABSTRACT: Monoamine oxidases play an integral role in brain function. Both monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) regulate neurochemistry by degrading monoamine neurotransmitters (serotonin, dopamine, and norepinephrine). Any alteration in MAO levels can have devastating effects on the brain and behavior by lowering or raising neurotransmitter levels and producing toxic reactive oxygen species. In this review article, MAO is examined in terms of function and genetic organization, with special focus on recent discoveries related to the transcriptional regulation of MAO. In recent studies, transcriptional regulation involves a repressor protein, R1, for MAO-A and an activator protein, KLF11 (a Krüppel-like factor; also referred to as transforming growth factor-beta early inducible gene 2, TIEG2), for both MAO-A and MAO-B, by binding to Sp/KLF sites in the core promoters of *MAO* and regulating *MAO* gene expression. Furthermore, KLF11 may influence MAO-B expression and augment glyceraldehyde-3 phosphate dehydrogenase (GAPDH) to upregulate MAO-B transcription upon exposure to ethanol. Finally, we review recent progress in MAO research and highlight the roles that MAOs play in several psychiatric conditions, including chronic stress, major depressive disorder and alcohol dependence. Further research in this area is needed to better understand MAOs, their transcription factors and signaling pathways in psychiatric illnesses in order to develop new strategies for pharmacological advancement.

Keywords: Monoamine oxidase, major depressive disorder, alcohol dependence, chronic stress, gene transcription, transcription factor, Krüppel-like factor 11 (transforming growth factor-beta-inducible early gene 2)

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1. Introduction

Psychiatric illness, including mood disorders and alcohol dependence, causes disturbance in personality, interferes with daily routines and damages personal relationships. Not since the advent of monoamine oxidase inhibitors (MAOIs) have we realized the important role monoamine oxidase (MAO) has in psychiatric conditions. In the 1950-60's, the discovery of MAO's impact on neurotransmitter metabolism followed by an upsurge in MAO research attempted to decipher the mechanisms underlying mental disorders, such as depression.

MAO has two isoforms, MAO-A and MAO-B. Serotonin (5-HT) and norepinephrine (NE) are preferentially deaminated by MAO-A while MAO-B primarily targets phenylethylamine (PEA) and benzylamine; however, both monoamine oxidases can degrade dopamine (DA). Though its role has been thoroughly documented in major depressive disorder, only recently have scientists discovered that MAO is also impacted in stress disorders and alcoholism. Additionally, aberrant MAO levels can result in other behavioral changes in addition to depressive moods; downregulation of MAO can manifest as aggressiveness as seen in MAO-knockout studies (*1*). Contrarily, upregulation of MAO results in rapid metabolism of neurotransmitters and consequently damages neurons partially through its byproduct, hydrogen peroxide. This holds implications for the neuronal damage seen in alcoholism, neurodegenerative disorders, and possibly one explanation for reduced cortical volume in chronically depressed patients. In this review study, we discuss MAO in terms of genetic organization and function, and emphasize recent discoveries on the transcriptional regulation of MAO and their implications in major depressive disorder and alcohol dependence.

2. Monoamine oxidase background

2.1. *Function*

Monoamine oxidase oxidizes amines from both endogenous and exogenous sources, thereby influencing the concentration of neurotransmitter amines as well as

many xenobiotics by controlling their availability and physiological activity (*2*). MAO-A and MAO-B belong to a family of flavin-containing amine oxidoreductases; both are located in the outer membrane of mitochondria (*3*), but are encoded by different genes (*4*). Although dopamine is primarily oxidized by MAO-B in humans and by MAO-A in rodents, in most species dopamine can be oxidized by both forms of the enzyme (*1*), just as serotonin can also be oxidized by MAO-B – though MAO-A has preference. MAO-A has higher affinity for serotonin, norepinephrine, dopamine, and the MAO inhibitor, clorgyline, whereas MAO-B has a higher affinity for phenylethylamine (a monoamine alkaloid that regulates the release of norepinephrine and dopamine), benzylamine (a common precursor of organic compounds), and the MAO inhibitors, deprenyl (*1*) and rasagiline (*5,6*). Exogenous sources of PEA and benzylamine require regulated entry into brain suggesting a functional role for MAO-B predominance at glial cells as a component of the blood-brain-barrier.

In light of the vital role that MAO plays in the metabolism of neurotransmitters, MAO-A dysfunction have been implicated in a variety of neuropsychiatric disorders such as depression, social anxiety, autism, and attention deficit hyperactivity disorder (*7*). Furthermore, MAO-A deficiency caused by a spontaneous mutation in the *MAO-A* gene in a Dutch family resulted in impulsive aggressive behavior and mild mental retardation in affected males (*8*). In addition, *MAO-A*, specifically, may act as a pro-apoptotic gene. MAO-A expression was shown to be increased in cells during nerve growth factor withdrawal-induced apoptosis, which inhibited neuronal proliferation and accelerated cell apoptosis through the p38 mitogen-activated protein kinase pathway (*9*).

These harmful effects of MAO-A (also MAO-B) are produced partially through the byproducts of their enzymatic activity (monoamine degradation) which include a number of neurotoxic species, such as hydrogen peroxide, ammonia, and MPP+ (1-methyl-4-phenylpyridinium, a neurotoxin that dysregulates NADH dehydrogenase). In particular, hydrogen peroxide can elicit the production of reactive oxygen species (ROS) and induce mitochondrial damage and neuronal apoptosis (*10*).

Unlike MAO-A, significant age-related increases in MAO-B activity may contribute to cellular degeneration in the brain due to corresponding increases in the production of ROS (*5,11*). However, MAO-A emerges first (*1*) and is near adult levels at birth while a several-fold increase in MAO-B activity occurs with aging (*12-14*). An increase in MAO-B with age has also been verified in human positron emission tomography (PET) studies in all brain regions examined (*15*). Abnormally elevated levels of MAO-B are well known to be associated with neurodegenerative diseases, such as Parkinson disease and Alzheimer disease (*16,17*). A consequence of increased MAO-B could result in elevated dopamine oxidation and byproducts, such as hydrogen peroxide, which form highly reactive hydroxyl radicals that subsequently damage proteins, membrane lipids, and nucleic acids leading to neuronal degeneration (*5*). In fact, hydrogen peroxide produced during the oxidative deamination of catecholamines produces damage to the mitochondrial membrane and DNA, which appears to be involved in the progression of neurodegenerative disorders, such as Parkinson disease (*11*).

2.2. *MAO genetic studies*

MAO-A and MAO-B share genetic homology and are highly conserved among species. Located in the outer mitochondrial membrane, MAO-A and MAO-B are encoded by two independent genes on chromosome Xp11.23-11.4 (*1,4,18,19*). These two genes consist of 15 exons and have identical exon-intron organization, which suggests that both *MAO-A* and *MAO-B* are derived from the duplication of a common ancestral gene (*1*). Interestingly, exon 12 products of *MAO-A* and *MAO-B* share 93.9% amino acid identity (*4*). Conversely, the arrangement of transcriptional promoters differs between the two monoamine oxidases. The *MAO-A* core promoter (0.14 kb) fragment lacks a TATA box, consists of three Sp1 (Sp/KLF) elements (*20,21*), and exhibits bidirectional promoter activity (*21*) whereas the *MAO-B* core promoter (0.15 kb) fragment consists of two clusters of overlapping Sp/KLF-binding sites separated by a CACCC element (*21*). The different promoter organization of *MAO-A* and *MAO-B* genes may underlie their different tissue- and cell-specific expression (*1*). Moreover, the conservation of these two genes indicates the biological importance of neurotransmitter regulation. This can be verified through the study of transgenic knockout (KO) mice.

In brains of MAO-A KO pups, serotonin concentrations were increased up to nine-fold compared with wild-type mice and in adult brains, serotonin levels were only increased two-fold due to the development of MAO-B (*1*). In the brains of MAO-A KO pups and adults, norepinephrine concentrations were increased up to two-fold, and a small increase in dopamine levels was observed in pup brains (*22*). Not surprisingly, the behavioral ramifications mimic the expression of neurotransmitters on a cellular level. Both MAO-A-deficient and MAO-B-deficient mice show an increased reactivity to stress in the forced-swim test (*1*). As norepinephrine and dopamine mediate the stress response and are further potentiated by phenylethylamine, these findings are consistent with elevated brain levels of norepinephrine and dopamine in MAO-A KO mice (*22*), and phenylethylamine in MAO-B KO mice (*23*). In addition to aberrant stress responses, MAO-A KO pups also exhibit aggressive behavior comparable to adults due to increased levels of serotonin; and this may

also be important for enhanced emotional learning that is exhibited by adult MAO-A KO mice (*24*). MAO-A and MAO-B double knockout mice exhibit reduced body weight, increased anxiety-like behavior and brain levels of serotonin, norepinephrine, dopamine, and phenylethylamine (*25*), increased baroreceptor response (*26*), and abnormal heart rate dynamics (*27*) compared to wild type mice. These studies illustrate a critical role of maintaining proper balance of MAO expression for normalcy in behavior and physiological responses. Additionally, forebrain-specific MAO-A transgenic mice generated from MAO KO mice using the calcium-dependent kinase IIα promoter showed restored axonal, cellular, and dendritic patterning in the forebrain similar to wild type mice and displayed decreased aggressive behavior compared to MAO-A KO mice without forebrain-specific MAO-A expression (*28*). These transgenic studies provide foundational knowledge of behavioral outcomes precipitated by gene knockout and results from these studies document the importance of monoamine oxidase not only for behavior, but for many other physiological functions.

3. Transcription factors for MAO-A and MAO-B

As with any gene expression, MAO regulation is determined by transcription factor interaction within the core promoter of *MAO*. The transcription factors can be activators, co-activators, or repressors depending on their influence on RNA polymerase. Ultimately, transcription factors will determine the level of gene expression by binding to unique domains inside the promoter with RNA polymerase II to form transcription initiation complexes.

3.1. *MAO-A transcription factors*

For *MAO-A*, an extensive repeat structure contained in two 90 bp repeats within the promoter sequence (1.2 kb upstream of the *MAO-A* coding sequences) downregulates human *MAO-A* promoter activity across ethnic groups and has been shown to affect the transcriptional activity of the *MAO-A* gene promoter in a luciferase assay system (*29*). This polymorphism constitutes a 30 bp repeated sequence, with 3-5 copies each for different individuals. Alleles with 3.5 or 4 copies of the repeat sequence are transcribed 2-10 times more efficiently than those with 3 or 5 copies of the repeat, suggesting an optimal length for the regulatory region (*29*). This is also shown *in vitro*, as median MAO-A activity in cell cultures with three repeats was significantly lower than that in cultures with four repeats (*20*), consistent with published evidence that *MAO-A* promoter constructs bearing three repeats have lower transcriptional activity in transfected neuroblastoma and choriocarcinoma cells (*29*). In fact, several studies have reported other various polymorphisms of *MAO-A*, including a GA repeat polymorphism in intron 2 and a G/T single-nucleotide polymorphism in exon 8 (*7*) on the X chromosome which may impact psychiatric or cognitive disorders. *MAO-A* may also have other genetic regulators not present on the X chromosome. Wu *et al*. recently found that *MAO-A* was regulated by a transcription factor encoded by the sex-determining region Y (SRY) gene located on the Y chromosome and that SRY and Sp1 form a transcriptional complex and synergistically activate *MAO-A* transcription (*7*). This occurs as Sp1 recruits SRY through physiological interaction, forming a transcriptional regulatory complex within the *MAO-A* core promoter capable of enhancing SRY-induced *MAO-A* gene expression. The influence of SRY on *MAO-A* expression shows sexual dimorphism, and this divergence has an important feature on neuronal activity, structure, and dysfunction with possible implications for neurodevelopmental disorders (*7*).

The human *MAO-A* core promoter region (-303/-64) contains four imperfect tandem repeats, with each repeat containing an Sp/KLF-binding site in reverse orientation with positive correlation existing between cellular Sp1 concentrations and *MAO-A* promoter and catalytic activities (*30*). This suggests *MAO-A* gene expression can be upregulated by Sp1. Sp1 is expressed ubiquitously in mammals (*31,32*) and is a key activator of the *MAO-A* promoter (*30*) by binding to GC-rich regions (*27*). Besides Sp1, two Sp-family proteins, Sp3 and Sp4, have also been shown to regulate the *MAO-A* promoter *via* the same Sp/KLF-binding sites (*7*). Sp4 activates the *MAO-A* core promoter like Sp1, while Sp3 may compete with Sp1 and Sp4 to repress *MAO-A* activation (*33*). A recently discovered novel transcription repressor, R1, has been show to downregulate *MAO-A* gene expression by competing with Sp1 for binding to Sp/KLF-binding sites as well (*34*).

3.2. *Novel MAO-A repressor, R1*

R1 (RAM2/CDCA7L/JPO2) is expressed widely in the human brain and peripheral tissues and includes a nuclear targeting sequence (aa 301-318) with a subcellular distribution in the nucleus, consistent with its functional role in the transcriptional regulation of MAO-A (*34*). R1, consisting of 454 amino acids with 77 amino acid residues in the C-terminal, shares 87% homology with the c-Myc target protein, JPO1 (*34*). c-Myc can act as a transcription factor and also plays a pivotal role in global chromatin structure by regulating histone acetylation. Therefore, R1 may interact with c-Myc in tumor genesis and cell division.

R1 directly impacts MAO-A expression. R1 binds to Sp/KLF-binding sites in the *MAO-A* core promoter and inhibits *MAO-A* promoter and catalytic activities (*34*). This notion is supported as Ou *et al*. demonstrated that R1 mRNA decreased 70%, 60%, and

45%, and MAO-A mRNA levels were increased by 2.5, 3.8, and 4.3-fold on days 1, 2, and 3, respectively, following serum starvation-induced apoptosis (*35*). R1 overexpression increases cell proliferation and decreases MAO-A activity whereas R1 knockdown by siRNA decreases proliferation and increases MAO-A mRNA (*35*), suggesting that R1 is upstream to MAO-A. Therefore, R1 overexpression prevents apoptosis, an event mediated by its repression of MAO-A. Thus, the pendulum shift between R1 and MAO-A has imperative roles in regulating the cell cycle and are negatively correlated in function and expression.

R1's role in cellular proliferation is further verified by immunostaining showing its colocalization with c-Myc, and that overexpression of c-Myc increases R1 mRNA. This increase is further escalated by inhibiting p38 MAPK in a concentration-dependent manner (*35*) as R1 is downstream to both c-Myc and p38. The interaction between R1 and c-Myc is co-operative in cell-cycle regulation. Furthermore, RT-PCR results show that cells transfected with R1 and/or c-Myc exhibited decreased MAO-A mRNA and increased E2F1 or cyclin D1 by 350-500%, demonstrating that E2F1 and cyclin D1 are also downstream of R1 (*35*).

These results show that MAO-A is not only involved in the oxidation of neurotransmitters but also plays a significant role in cellular development. Since the byproduct of MAO-A activity is hydrogen peroxide (H_2O_2) resulting in cytotoxic stress which causes cell death, R1 may therefore prevent cells from undergoing apoptosis. Understanding the mechanics of up/downstream signaling pathways will allow greater insight into MAO-mediated apoptosis. Further research to elucidate this transcription factor, R1, its signaling pathway, and regulators in detrimental conditions such as mental illness could explain morphological changes in the brain that have been unaccounted for.

3.3. *Novel MAO-A activator, KLF11 (TIEG2)*

Krüppel-like factor 11 (KLF11), also referred to as transforming growth factor-beta-inducible early gene 2 (TIEG2), is a member of the Sp/KLF family of transcription factors. KLF11 can inhibit cell growth by acting as a potential effector of the transforming growth factor β (TGFβ) signaling pathway and increases the rate of apoptosis in KLF11 transgenic pancreatic cells (*36*). Aside from its role in cell-cycle regulation, KLF11 has recently been reported to act as a transcriptional activator of *MAO-A*. In addition, glucocorticoid exposure can further amplify KLF11 expression and influence KLF11-induced *MAO-A* transcriptional activation (Figure 1A). In brain-derived SH-SY5Y cell lines, treatment with dexamethasone, a synthetic glucocorticoid, resulted in a 2.3-fold increase in KLF11 expression and 3.3-fold increase in nuclear fraction (*37*), suggesting increases in both KLF11 protein levels and translocation to the nucleus in the presence of dexamethasone. Examining the significance of KLF11 action on MAO-A, cells stably transfected with KLF11 showed a 2-fold increase in MAO-A mRNA levels and a 4.2-fold increase in MAO-A mRNA following dexamethasone treatment compared to control vector (*37*). Interestingly, when cells were treated with KLF11-

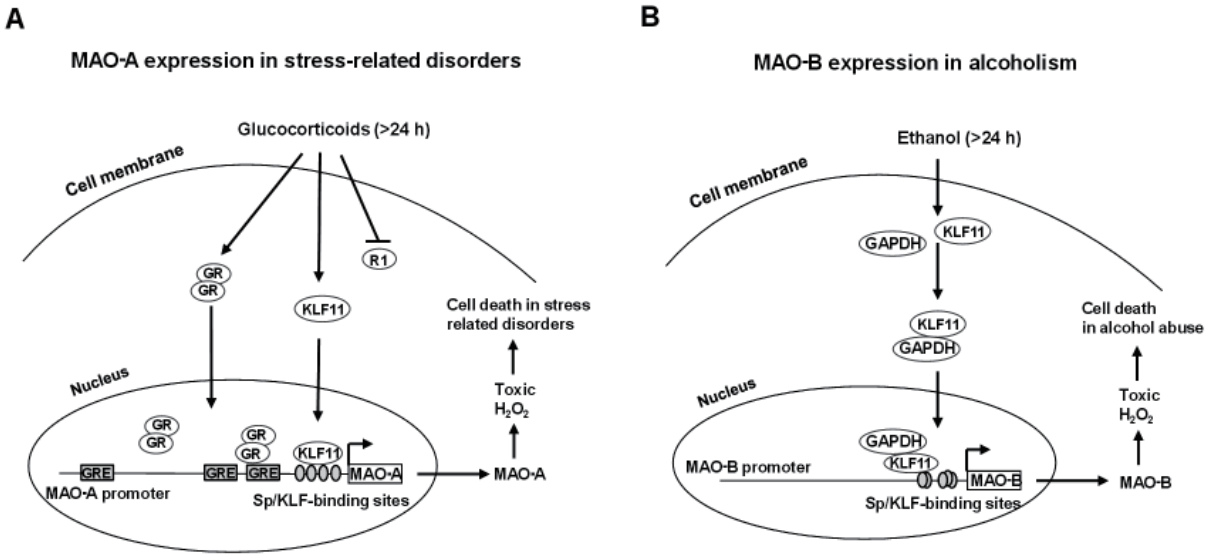

Figure 1. A representative structure of the transcriptional regulation of *MAO-A* gene expression (A) in stress-related disorders and *MAO-B* gene expression (B) in alcohol-related disorders. (A) The human *MAO-A* promoter contains glucocorticoid response element (GRE) and Sp/KLF-binding sites, both of which are independently responsive to the impact of glucocorticoids on MAO-A upregulation. **(B)** The human *MAO-B* promoter contains Sp/KLF-binding sites, which are responsive to ethanol-induced GAPDH/KLF11-mediated upregulation of MAO-B and subsequent cellular toxicity. Arrows and dashed line indicate activation and repression of the following targets, respectively. R1: a transcriptional repressor; GR: glucocorticoid receptor; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; KLF11: Krüppel-like factor 11 (also called TIEG2).

siRNA to deplete endogenous KLF11, dexamethasone-induced MAO-A expression was reduced by 30% compared to control-siRNA cells showing that KLF11 mediates corticoid-induced upregulation of MAO-A (*37*).

KLF transcription factors have been shown to interact with histone acetyl transferases (HATs), such as p300, to regulate transcription. To further evaluate how KLF couples to chromatin remodeling machines, cells were transiently co-transfected with a p300 and KLF11 expression constructs in the *MAO-A* promoter-luciferase reporter gene which showed that activation of *MAO-A* by KLF11 was greatly increased when co-transfected with p300 (*37*). Therefore, successful augmentation of KLF11 by this particular HAT shows that glucocorticoids act through KLF11 to upregulate *MAO-A* promoter activity, and this pathway is mediated by a p300-dependent mechanism. Furthermore, rats exposed to chronic social defeat stress revealed a significant increase of both MAO-A and KLF11 levels in the brain cortex compared to the untreated control rats, providing further *in vivo* data that KLF11 is a novel activator for *MAO-A* (*37*).

3.4. *MAO-B transcription factors*

The human *MAO-B* core promoter (0.15 kb) fragment contains two clusters of overlapping Sp/KLF-binding sites separated by a CACCC element, and a TATA box (*21,38*). Among others, modulators of MAO-B expression include DNA status and hormonal influence. DNA methylation of CpG sites in the *MAO-B* promoter epigenetically inhibits *MAO-B* gene expression (*39*) as these regions become silenced. In addition, glucocorticoids and glucocorticoid receptors upregulate MAO-B transcription through the fourth glucocorticoid response element of the *MAO-B* promoter, which has been recently found to overlap with a consensus retinoic acid response (RAR) element suggesting the potential regulation of MAO-B by retinoic acid (*40*). Moreover, retinoic acid activates MAO-B transcription through RAR-α and the third RAR element in the *MAO-B* promoter as RAR-α physically interacts with Sp1 *via* zinc finger domains in Sp1 (*40*). Collectively, these known regulators exhibit the complexity underlying MAO-B expression. Still, many elements are unknown about the functionality of these regulators in different environmental conditions, such as retinoic acid/*MAO-B* interaction during development and Sp-family/*MAO-B* interactions in psychiatric illness.

MAO-B gene expression can also be regulated through signaling pathways. For example, phorbol-12-myristate-13-acetate (PMA), an extracellular stress inducer, increases human MAO-B expression. PMA transiently increases *Egr-1* and *c-Jun* gene expression *via* protein kinase C and MAPK signaling pathways, including Ras, MEK1, MEK3, MEK7, ERK2, JNK1, and p38/RK (*41*). Site directed mutations show that Egr-1 and c-Jun then transactivate the *MAO-B* promoter and increase endogenous MAO-B transcripts *via* the Sp1/Erg-1/Sp1 overlapping binding sites (*41*). Additionally, protein kinase C inhibitor blocks the PMA dependent activation of *MAO-B* indicating that MAO expression is selectively induced by the activation of protein kinase C and MAPK signaling pathways and that c-Jun and Egr-1 appear to be the ultimate targets of this regulation (*41*).

The Sp-family proteins also demonstrate a significant impact on MAO-B transcriptional regulation. Analysis of nine site-directed mutations exhibiting the highest activity at -246/-99 region reveals that both clusters of Sp/KLF-binding sites contribute positively whereas the CACCC element contributes negatively to transcriptional activity (*42*). Sp1 can activate the *MAO-B* core promoter *via* Sp/KLF-binding overlapping sites, and its activation is repressed by Sp3 interaction as determined by gel shift analysis (*34,42*) just as *MAO-A*. Furthermore, Sp4 can trans-activate *MAO-B* promoter activity *via* Sp1 clusters suggesting that the binding to overlapping Sp1 sites by various members of the Sp family is important for the upregulation of *MAO-B* gene expression, whereas over-expression of Sp3 or BTEB2, an Sp3-related family member, can repress activation (*38*). Sp3 is a ubiquitously expressed transcription factor, closely related to Sp1 but, unlike Sp1, often functions as a transcriptional repressor by means of interacting with GC-rich Sp/KLF-binding sites (*43,44*). Sp3 has no net effect on *MAO-B* gene expression as it *i*) represses the transcription of the human *MAO-B* gene by interaction with the CACCC box, *ii*) activates *MAO-B* through proximal overlapping Sp1 sites, and *iii*) has bi-functional regulation with independent modular repressor and activator domains (*42*). KLF11 also influences the expression of MAO-B (*42*).

3.5. *Novel MAO-B activator, KLF11 (TIEG2)*

Studies have shown that KLF11 (TIEG2) represses gene transcription and regulates cell growth, development and differentiation (*45*) by binding to GC-rich Sp/KLF-binding sites (*46,47*). In addition to *MAO-A* transcriptional activation, KLF11 has recently been shown to activate *MAO-B* gene expression (*42*), which implicates that one function of MAO-B may serve as an anti-proliferating mechanism. KLF11 reportedly inhibits cell growth (*46*) and mediates caspase-3-dependent apoptosis (*48*). Depending on where KLF11 binds within the promoter will influence how MAO-B is expressed. KLF11 serves as a repressor when binding through the CACCC element but as an activator when binding through proximal Sp/KLF-binding sites (*42*). Thus, KLF11 serves dual functions as both a regulator of cell-cycle-dependent activities and as a transcriptional activator for both *MAO-A* and *MAO-B*.

4. Implications for MAO in psychiatric illness

4.1. *Impact of stress on MAO*

Chronic stress encompasses the psychological perturbations that affect the normal physiological state of the body and interferes with emotional, cognitive, and physical aspects of health. Often, stress may precipitate or present comorbidly with depression. A major response to stress is the production of glucocorticoids, steroid hormones secreted from the adrenal zona fasciculata, which play a crucial role in sympathetic arousal, immunity, and behavior. Excessive glucocorticoid exposure can result in neuronal cell death and dysregulation as an abnormal increase of glucocorticoid levels has been associated with atrophy of the hippocampus (*49*) and major depression (*50*). Additionally, stress has been correlated with increased salivary activity of MAO-A and MAO-B (*51*). Stress may also impact the expression of monoamine oxidases, further decreasing monoamine availability in depression.

As MAO and glucocorticoid hypersecretion are associated with depression, the synthetic glucocorticoid, dexamethasone, has been documented to increase MAO-A activity but decrease the MAO-transcriptional repressor, R1, in human neuroblastoma and glioblastoma cells through its role as a cellular stressor (*52*) (Figure 1A). For example, dexamethasone administration to older Sprague-Dawley rats can increase MAO-A density in the brain by 300% (*53*), and dexamethasone has been shown to increase MAO-A mRNA, protein, and enzymatic activity in human skeletal muscle cells (*54*). Furthermore, dexamethasone increases MAO-A in the dorsal raphe nucleus in rats (*55*), induces MAO-B expression and activity in both neuronal cells (*56*) and astrocytes (*57*), and ultimately reduces the number of viable brain cells (*58*).

The biological action of glucocorticoids and androgens are mediated through their respective receptors, glucocorticoid receptor (GR) and androgen receptor (AR) (*12*). GR and AR undergo dimerization before binding to a specific region in their promoter responsible for gene expression, the glucocorticoid response element (GRE) and the androgen response element (ARE), respectively. There are three consensus GRE/AREs and a core promoter with four Sp/KLF-binding sites that have been identified within the human *MAO-A* 2 kb promoter region (Figure 1A); Ou *et al*. reported that deleting the third GRE/ARE reduced the glucocorticoid effect compared to that of wild type upon dexamethasone exposure, yet still showed an increase in *MAO-A* promoter activity as compared to cells not treated with dexamethasone. These results suggested that the third GRE/ARE element was important for the GR activation (*52*). In the case of MAO-B, four consensus GREs have been identified in the *MAO-B* 2 kb promoter and GRs directly bind to GRE4 (*59*). Much like *MAO-A*'s third GRE, glucocorticoid complexes may target a particular region within the promoter. In addition, Sp/KLF-binding sites in the *MAO-B* core promoter are also necessary for glucocorticoid activation of the *MAO-B* promoter as deletion of Sp/KLF-binding sites downstream of GRE4 reduced *MAO-B*'s response to glucocorticoids (*59*). Indeed, Sp1 appears to be a key player in glucocorticoid regulation over MAO-B as removal of GRE in the core promoter still results in glucocorticoid-inducible MAO-B upregulation (*59*). Glucocorticoids also show an ability to directly interact with basal transcription factors, such as TATA-binding protein, transcription factor IIB (TFIIB) and other co-activators. To counteract the effect of glucocorticoids, R1 is shown to compete with Sp1 for binding to Sp/KLF-binding sites in the *MAO-B* core promoter, thereby exerting repressing effects on MAO-B (*59*). In fact, overexpression of E2-F associated phosphoprotein (EAPP), a ubiquitous nuclear protein, and R1 reduces both basal and Sp1-enhanced glucocorticoid activation (*59*), suggesting cell-specific events may supersede the action of glucocorticoids.

Chronic stress may result in long-lasting changes in the brain due to elevated levels of MAO including increased cell death due to the presence of ROS. As a result, an MAO inhibitor prevents cell death related to this manner of toxicity (*60*). M30, a new inhibitor of MAO, has recently demonstrated its effectiveness in neuroprotection by significantly decreasing the enzymatic activity of both MAO-A and MAO-B in human neuroblastoma cells while also decreasing the amount of fragmented DNA due to ROS production and increasing cell viability in stressful environments (*61*). Compared to rasagiline and selegiline, which are irreversible MAO-B inhibitors, M30 had the highest neuroprotectivity by providing the greatest decrease in cell death rates and MAO-A activity following dexamethasone-induced toxicity (*61*). In light of the neuroprotective advantages MAO inhibitors provide, newer generations of MAO inhibitors, currently used for the treatment of depression and neurodegenerative diseases, may be potential drug candidates for alleviating the toxic, pejorative effects of increased MAO-A and MAO-B in chronic stress.

4.2. *MAO-A in depression*

Major depressive disorder (MDD) has a lifetime prevalence of 16.6% (*62*), making it an important topic of research and necessitating new pharmacological targets in clinical treatment. Since resistance to treatment and recurrence of major depressive episodes constitute a large portion of the MDD burden, it is important to evaluate monoamine dysregulation during and after selective serotonin re-uptake inhibitor (SSRI) treatment. Moreover, the MAO theory of depression is

bolstered since SSRI's have no direct effect on MAO's and work secondarily on transporters that are responding to changes in monoamine concentration. Meyer *et al*. were able to demonstrate that greater MAO-A binding during major depressive episodes persists after short-term SSRI treatment and is greater during recovery from MDD (*63*). This supports an ongoing monoamine-lowering process due to pathological conditions that is not entirely counterbalanced by SSRI treatment. From the perspective of the monoamine theory, SSRIs raise serotonin levels vigorously (*64*), whereas elevated MAO-A levels would be expected to metabolize serotonin and other monoamines readily. The high recurrence rates of major depressive episodes following short-term SSRI treatment indicate the power of MAO-A on the monoamine-lowering process. With MAO-A binding greater during recovery, an underlying impaired ability to regulate monoamines is present competing to lower monoamine concentrations which have been increased by SSRI treatment. Hence, the mismatch between monoamine levels raised by treatment and monoamine levels lowered by disease processes might, at times, contribute to a lack of response to SSRI treatment (*63*). Another aspect to consider in MAO theory is that MAO-A metabolism creates ROS that are potentially neurotoxic if present in excess, such as hydrogen peroxide. This could be one explanation for dendritic loss, cortical shrinkage, and neuronal apoptosis associated with MDD.

A promising avenue to depict human MAO-A density and distribution *in vivo* during a major depressive episode is using positron emission tomography (PET) with harmine-labeled carbon 11 ([11C]harmine), a selective, reversible PET radio tracer with high affinity for the MAO-A enzyme, showing high brain uptake in humans with the greatest uptake in regions with the highest MAO-A density. Meyer *et al*. reported that MAO-A density was elevated throughout the brain on average by 34% in MDD patients compared to controls, with the highest densities in the thalamus and cingulated cortex (*65*). These areas are of great significance as the thalamus, particularly the ventral posterolateral segment, has many acetylcholinergic projections containing MAO-A. The anterior nucleus has connections with the cingulate gyrus and the dorsomedial nucleus projects to the frontal lobe, both of which are implicated in mood processes. With no other studies explaining why monoamine levels are lower during a depressive episode, it is thereby plausible that an elevation in brain MAO-A density is the primary monoamine-lowering process during major depressive episodes (*65*).

Genetic polymorphisms may also contribute to MAO-A expression and lower levels of neurotransmitters seen in depression. The MAO-A coding gene (Xp11.4-Xp11.3) presents a well-characterized variable number tandem repeat (VNTR) functional polymorphism in the promoter region, which has two common alleles that selectively influence protein transcription and, hence, enzymatic activity (*66*). Beyond environmental factors, proof exists that innate genetic polymorphisms may ultimately impact susceptibility of psychiatric illness.

The role of R1 in MDD has only recently been investigated. As R1 is a novel repressor of MAO-A and is also involved in cell cycle regulation, further research to elucidate their activity in mental illness is needed to determine whether morphological changes in the brain are contributed by R1. To support this notion, Johnson *et al*. reported a decrease in R1 by 37.5% and an increase in MAO-A levels by 40% in human postmortem prefrontal cortices diagnosed with major depressive disorder (MDD) who had not undergone antidepressant drug therapy (*67*). Additionally, R1 levels in depressed individuals receiving antidepressants had comparable levels of R1 to that of non-medicated depressed, suggesting that current antidepressants do not significantly modulate R1 levels. These results corroborate the notion reported by Meyer *et al*. that antidepressant treatments do not adjust MAO-A binding even after 6 weeks of SSRI treatment but only compensate increased MAO-A expression by amplifying neurotransmitter levels at the synapse. With results indicating elevated MAO-A-binding and reduced R1 levels *in vivo*, and that current antidepressant treatments have no significant impact on the oxidation of monoamines, future research on R1 as a diagnostic tool and pharmacological target is justified.

4.3. *MAO-B in alcoholism*

Alcoholism is a substance use disorder with a lifetime prevalence of 14.6% (*62*) that results in cognitive impairments and brain cell loss. It is also a major psychiatric condition that causes approximately one-half of alcoholics to suffer from neuropsychological difficulties (*68,69*) that affect physical health and memory along with social, family, and job responsibilities (*70,71*). Ethanol also induces neuronal cell death and cell cycle delay in cell model systems *in vitro* (*72-74*). Furthermore, alcohol-use disorders have been shown to reduce prefrontal cortex volume as compared to healthy controls (*75*) and lower densities of neuronal and glial cells in brains from human subjects with alcohol dependence (*76,77*). In addition, MAO-B has been implicated in alcoholism (*78*) and until recently, it was unclear exactly how MAO-B was involved. As previously discussed, MAO-B can generate ROS from the breakdown of biogenic amines, and is upregulated in response to KLF11 (TIEG2) binding at the core promoter region of *MAO-B* promoter. Therefore, the KLF11(TIEG2)-MAO-B cascade has a role in cell dysfunction and damage (*79*) related to alcohol use disorders.

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is a multifunctional protein that catalyzes and breaks down glucose with the release of energy and carbon (*80*), occurring during the 6th step of glycolysis. Recently, GAPDH has been implicated in other non-metabolic roles involving the initiation of apoptosis and transcriptional regulation. Furthermore, the protein level of GAPDH was not only increased in the prefrontal cortex of brains from human alcoholics (*81*), but also elevated in rat brains that were exposed to ethanol (*79*). To examine the relationship between GAPDH and the KLF11-MAO-B cascade, Ou *et al*. treated human brain cell lines with ethanol and found that MAO-B mRNA levels were significantly increased by 4-fold and GAPDH was increased 3.5-fold in the nucleus with a 1.8-fold increase overall following ethanol treatments (*79*). Under these conditions, GAPDH-KLF11 co-immunoprecipitation was increased in the nucleus, levels of GAPDH interacting with KLF11 were increased, and KLF11-elicited *MAO-B* gene transcription is enhanced more by the coexpression of GAPDH (*79*). These results indicate that GAPDH can increase MAO-B *via* KLF11 in the presence of ethanol by translocating to the nucleus where it binds to KLF11 and augments KLF11-mediated gene transcription for *MAO-B* at Sp/KLF binding sites (*79*), thereby resulting in subsequent cell damage in neuronal cells exposed to ethanol due to increased MAO-B-mediated oxidative stress (Figure 1B). Remarkably, ethanol exposure in the presence of an MAO-B inhibitor (deprenyl) reduced the expression of both KLF11 and MAO-B and increased cell viability (*60*). Moreover, a new MAO-B inhibitor (rasagiline) and its metabolite could decrease ethanol-induced cell death by preventing nuclear translocation of GAPDH in cell cultures *in vitro* (*80*).

In vivo studies examining the prefrontal cortex (PFC) from postmortem subjects with alcohol dependence showed a significant increase in protein levels of GAPDH and MAO-B compared to normal subjects while ethanol-preferring rats showed a two-fold increase in GAPDH and a 1.7-fold increase in MAO-B protein in the PFC when exposed to ethanol for 4 weeks (*82*). Interestingly, rats treated chronically with ethanol not only showed an increase in GAPDH and MAO-B protein levels, but also resulted in a 1.6-fold increase of KLF11, a 1.37-fold increase in MAO-B catalytic activity, and a 1.8-fold increase in active caspase 3, an apoptotic protein, in the PFC compared to control rats (*74*). Conversely, the anti-apoptotic protein, Bcl-2, was decreased by 41% in rats exposed to ethanol compared to controls (*82*). The decrease in anti-apoptotic Bcl-2 and increase in apoptotic caspase 3 in the PFC of rat brains upon ethanol exposure suggest that ethanol induces apoptosis that may be mediated by an increase in the KLF11-MAO-B cell death cascade (*82*). The GAPDH-KLF11-MAO-B cascade is a novel approach for explaining ethanol-induced neuronal death due to chronic alcoholism. However, the precise mechanism for GAPDH-mediated damage in alcoholism and upstream effectors of GAPDH in this context remains elusive.

5. Conclusion and future directions

Monoamine oxidases play a fundamental role in brain homeostasis by regulating neurotransmitters which has been substantially documented in literature. However, improper levels of monoamine oxidase can otherwise damage the brain and impact behavior. Because finding the proper balance in MAO expression is paramount, any deviation can result in significant impairment or psychiatric illness. For example, since MAO-A and MAO-B catalytic activity produces neurotoxic hydrogen peroxide and nitrogen species resulting in oxidative damage to mitochondrial DNA, they hold implications for apoptosis, neuronal aging, neurodegenerative diseases, mental illness, and developmental disorders. Furthermore, if R1 acts as an anti-apoptotic force and reduced levels of R1 have been verified in postmortem brains of individuals diagnosed with major depressive disorder, then it is plausible that decreased R1 could attribute to not only a loss of monoamines, but increased neuronal apoptosis and dendritic loss associated with depression. Further studies to investigate the extent of cortical shrinkage as a result of R1 are necessary. Likewise, studies to measure the extent of brain tissue injury and axonal deterioration as a result of increased KLF11, MAO activity and oxidative stress associated with alcohol dependence are also warranted. Many important MAO transcription factors have been recently discovered; however, it remains unclear how these factors function in response to many physiological changes, hormonal influences, age, cortical organization and neurodevelopment, metabolic changes, downstream neurotransmitter pathways, cellular signaling pathways, and current antidepressant medications.

Since MAO downregulation does not adequately occur with current antidepressant treatment regimens, it could be possible that maintaining a normal level of neurotransmitter at the synapse for an extended period of time could adjust or "reset" MAO expression *via* upstream or downstream regulatory pathways, endocrine responses, or neuronal resurgence, and also involve individual genetic backgrounds. If MAO upregulation is the first step towards a monoamine-lowering process during depressive disorders, such as major depressive disorder, it makes sense that MAO downregulation would be the last step involved in a pathological recovery process. To elucidate this notion, many signaling and second messenger pathways would need to be studied in relation to their impact on MAO transcription factors. Finally, pharmacological targeting of aforementioned molecular pathways in major depressive disorder and alcoholism could provide

tremendous benefits for treatment and prognosis. Alternative pharmacological approaches could involve gene therapy with siRNAs, specific drug targeting of transcription factors and the development and application of newer generation MAO inhibitors. Much work is still needed in the field of MAO research; although, new advancements in our understanding of MAO related to psychiatric illness will be fruitful for future research directions and clinical outcomes.

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