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BEHAVIORAL OUTCOMES OF MONOAMINE OXIDASE DEFICIENCY: PRECLINICAL AND CLINICAL EVIDENCE

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Abstract

Monoamine oxidase (MAO) isoenzymes A and B are mitochondrial-bound proteins, catalyzing the oxidative deamination of monoamine neurotransmitters as well as xenobiotic amines. Although they derive from a common ancestral progenitor gene, are located at X-chromosome and display 70% structural identity, their substrate preference, regional distribution, and physiological role are divergent. In fact, while MAO-A has high affinity for serotonin and norepinephrine, MAO-B primarily serves the catabolism of 2-phenylethylamine (PEA) and contributes to the degradation of other trace amines and dopamine. Convergent lines of preclinical and clinical evidence indicate that variations in MAO enzymatic activity—due to either genetic or environmental factors—can exert a profound influence on behavioral regulation and play a role in the pathophysiology of a large spectrum of mental and neurodegenerative disorders, ranging from antisocial personality disorder to Parkinson's disease. Over the past few years, numerous advances have been made in our understanding of the phenotypical variations associated with genetic polymorphisms and mutations of the genes encoding for both isoenzymes. In particular, novel findings on the phenotypes of MAO-deficient mice are highlighting novel potential implications of both isoenzymes in a broad spectrum of mental disorders, ranging from autism and anxiety to impulse-control disorders and ADHD. These studies will lay the foundation for future research on the neurobiological and neurochemical bases of these pathological conditions, as well as the role of gene × environment interactions in the vulnerability to several mental disorders.

I. General Characteristics of Monoamine Oxidase

A. Catalytic Reaction

Monoamine oxidases [MAOs; amine: oxygen oxidoreductase (deaminating) (flavin-containing); EC 1.4.3.4] are a family of mitochondrial-bound flavoproteins catalyzing the oxidative deamination of monoamine neurotransmitters, neuro-modulators, and hormones to the corresponding aldehydes:

$$RCH_2NH_2+O_2+H_3O^+ \rightarrow RCHO+NH_4^+ +H_2O_2$$

This reaction requires flavin adenine dinucleotide (FAD) as a covalently bound redox cofactor and consists of three main steps (for a detailed analysis of the current knowledge on the catalytic mechanisms of MAO, see Edmondson *et al.*, 2009):

1. Following the formation of a FAD-substrate adduct, the cofactor is reduced to its hydroquinone form ($FADH_2$), while the amine is converted into the corresponding imine.

$$\text{Enz}-\text{FAD}+\text{RCH}_2\text{NH}_2 \rightarrow \text{Enz}-\text{FADH}_2+\text{RCH}=\text{NH}$$

2. Once dissociated from the enzyme, the imine is spontaneously hydrolyzed, with production of aldehyde and ammonium:

$$\text{RCH}=\text{NH}+\text{H}_3\text{O}^+ \rightarrow \text{RCHO}+\text{NH}_4^+$$

3. FADH2 is reoxidized to FAD, with formation of hydrogen peroxide from molecular oxygen. This reaction is the rate-limiting step of the whole enzymatic process:

$$\text{Enz}-\text{FADH}_2+\text{O}_2 \rightarrow \text{Enz}-\text{FAD}+\text{H}_2\text{O}_2$$

As shown in Table I, the endogenous substrates of MAO include key brain neurotransmitters, such as serotonin (5-hydroxytryptamine, 5-HT), dopamine (DA), norepinephrine (NE), and epinephrine (E), as well as a number of trace amines, such as tyramine, tryptamine, 2-phenylethylamine (PEA), octopamine, and 3-iodothyronamine (T1AM). Notably, the oxidative deamination of short-chain primary amines (including PEA, tyramine, and T1AM) is not exclusively mediated by MAO but also contributed by the copper/topaquinone-containing semicarbazide-sensitive amine oxidase (SSAO; encoded by the gene *AOC3*; Obata, 2002; Saba *et al.*, 2010). The role of MAO in the homeostasis of these compounds is essential to modulate the neuroendocrine regulation of the central nervous system and many peripheral organs.

The aldehydes produced by MAO are toxic species (for a review on the pathogenic potential of aldehydes, see O'Brien *et al.*, 2005) which need to be converted in less harmful metabolites. Thus, this enzyme is functionally coupled with a NAD(P)^+-dependent aldehyde dehydrogenase (ALDH), which oxidizes the aldehyde to the corresponding carboxylic acid; alternatively (depending on the location and the intracellular conditions), aldehydes can be reduced to alcohols or glycols by aldehyde reductase (ALR) or alcohol dehydrogenase (ADH) (Table I). The main metabolic pathway of 5-HT consists in the conversion of this mono-amine into 5-hydroxyindolacetic acid (5-HIAA) by joint action of MAO and ALDH. Like other MAO metabolites, 5-HIAA is rapidly eliminated by diffusion into the bloodstream and excreted through the kidneys by glomerular filtration and active tubular excretion (Udenfriend *et al.*, 1956; Despopoulos and Weissbach, 1957). Given the predominance of the MAO-ALDH pathway in 5-HT metabolism, urinary levels of 5-HIAA are used as an index for measurement of plasma 5-HT content (with diagnostic value as a biomarker for carcinoid syndrome, a paraneoplastic disorder caused by gastrointestinal apudomas secreting 5-HT). Small amounts of 5-HT (1–5%) are converted into 5-hydroxyindolethanol (5-HIET, also termed 5-hydroxytryptophol) by either ALR or ADH (Feldstein and Williamson, 1968; Beck *et al.*, 1984; Consalvi *et al.*, 1986; Svensson *et al.*, 1999) (Table I). Interestingly, the amount of 5-HIET can be enhanced by compounds that compete with endogenous 5-HT metabolite for ALDH, such as ethanol (Helander *et al.*, 1993).

The metabolism of catecholamines (DA, NE, E) is served by both MAO (in conjunction with either ALDH or ALR) and catecholamine-*O*-methyl-transferase (COMT). The combined action of the two enzymes converts DA into either homovanillic acid (HVA; MAO/ALDH + COMT pathway) or, less frequently, into 3-methoxy-4-hydroxyphenylethanol (MHPE; MAO/ALR + COMT pathway). The latter can be processed by ADH into HVA (Fig. 1).

NE and E undergo similar degradation pathways (Fig. 2). Specifically, MAO converts both monoamines into 3,4-dihydroxyphenylglycol aldehyde (DOPGAL), which is further processed by ALR into 3,4-dihydroxylphenylethylene glycol (DOPEG). A much smaller aliquote of DOPGAL is oxidized to 3,4-dihydroxymandelic acid (DOMA). COMT converts DOPEG into 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) and DOMA into vanillyl mandelic acid (VMA). Alternatively, NE and E can be methylated by COMT to normetanephrine and metanephrine, respectively. These metabolites can be conjugated with sulfate groups by sulfatransferase 1A3 (SULT1A3) or processed by either MAO/ALR or MAO/ALDH into MHPG and VMA.

MAO function is highly critical for the regulation the intracellular redox state in neurons and other cells; indeed, one of the byproducts of MAO-mediated reaction, hydrogen peroxide, is a potent oxidizer which can trigger the formation of superoxide radicals and other reactive oxygen species, which can in turn induce mitochondrial and cytoplasmic damage. Under physiological conditions, the overall redox potential is kept in equilibrium by antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase; nevertheless, high concentrations of ammonia (the other by-product of the reaction) have been shown to decrease the activity of these enzymes and lead to the formation of superoxide radicals (Kosenko *et al.*, 1997). The excess of oxidizing species in the central nervous system leads to permanent damages through death of neurons and glia. These mechanisms lay the theoretical foundations for the implication of MAO in the pathophysiology of certain neurodegenerative disorders, such as Parkinson's disease (PD) and dementias (Danielczyk *et al.*, 1988). In line with this concept, an increase in the activity of the isoenzyme MAO-B in platelets has been found in Alzheimer's disease patients, leading to the proposal that this parameter may be an early biomarker for diagnosis of this condition (Grünblatt *et al.*, 2005).

Finally, MAO serves a primary role in the degradation of primary, secondary, and some tertiary xenobiotic amines, which is particularly important to preventing their cardio- and neurotoxicity. A well-characterized example of these detrimental effects is the "cheese reaction," a vasoconstrictive crisis (often lethal) caused by the absorption of sympathomimetic amines in fermented food (such as cheese, wine, etc.) following administration of irreversible MAO inhibitors (Anderson *et al.*, 1993).

B. MAO Isoenzymes

In higher vertebrates, the MAO family comprises two isoenzymes, termed A and B, which, despite a substantial structural overlap, are remarkably different for substrate preference, inhibitor selectivity, anatomical distribution, and functional role in behavioral regulation.

The existence of multiple MAO isoenzymes was initially postulated to account for a number of experimental data indicating divergent neurochemical effects of different inhibitors. Indeed, MAO-A is selectively blocked by low doses of clorgyline (Johnston, 1968), while MAO-B is inhibited by nanomolar concentrations of (*R*)-deprenyl (Knoll and Magyar, 1972). The two isoenzymes can be separated electrophoretically (Shih and Eiduson, 1969; Youdim *et al.*, 1969).

Subsequent studies showed that MAO-A had very high affinity for 5-HT (120 folds higher than MAO-B) and, to a lower degree, NE; by contrast, MAO-B preferred PEA and benzylamine as its substrates. The degradation of DA, tryptamine, and tyramine is mediated by both MAOs, but the relative contribution of each isoenzyme appears to vary greatly in relation to the species and the tissue under consideration. For example, DA metabolism is prevalently served by MAO-A in rodents and by MAO-B in humans and other primates (Garrick and Murphy, 1980; Fornai *et al.*, 1999). The dichotomy between MAO-A and -B in terms of substrate preference is not absolute; in fact, in the absence of one isoenzyme, the

other can deaminate a certain amount of its nonpreferred mono-amine substrates (Chen *et al.*, 2004). This mechanism of partial compensation mechanism is fully revealed by the neurochemical outcomes of MAO deficiency in murine models (see below) and indicates the physiological significance of the presence of two isoenzymes *in vivo*. The unequivocal demonstration of the existence of two isoenzymes came in 1988, with the cloning of human *MAO-A* and *MAO-B* genes (Bach *et al.*, 1988). Subsequent studies elucidated the structural configuration of both genes, revealing that they are located on the locus Xp11.23, in a tail-to-tail arrangement, with the 3′-coding sequences separated by about 50 kb (Ozelius *et al.*, 1988; Lan *et al.*, 1989a,b; Levy *et al.*, 1989; Chen *et al.*, 1992). *MAO-A* and *MAO-B* encode for two proteins of 527 and 520 amino acids, with molecular weights of 59.7 and 58.8 kDa, respectively. Interestingly, the two genes share ~70% sequence identity and an identical intron–exon organization, with 15 exons and 14 introns; these findings provided one of the first lines of evidence to define the structure and evolution of the isoenzymes, by suggesting that both genes derive from duplication of a common ancestor gene (Grimsby *et al.*, 1991). In agreement with this interpretation, numerous phylogenetic studies have revealed the existence of only one MAO in early eukaryotes (Schilling and Lerch, 1995), invertebrates (Boutet *et al.*, 2004), and teleost fish (Chen *et al.*, 1994; Setini *et al.*, 2005; Anichtchik *et al.*, 2006). Conversely, the presence of two MAO isoenzymes can be traced back to anuran amphibians (Kobayashi *et al.*, 1981); in frogs, MAO-A is predominant in the tadpole stage, while MAO-B expression increases through metamorphosis (Nicotra and Senatori, 1988), pointing at the possibility that the duplication of the gene may have been selected as an advantageous trait to maintain redox homeostasis in response to the development of lung-based respiration and the consequent hyperoxic shift. Interestingly, MAO-B has a much higher K_m (lower affinity) for O_2 (~ 250 μM) than MAO-A ~ (6 μM) (Edmondson *et al.*, 2004). Given the role of monoamines in the regulation of cardiovascular function, the development of substrate-selective isoenzymes may have also been instrumental to withstand the new challenges posed by terrestrial life to blood circulation.

A more detailed insight in the structural characteristics of MAOs was afforded by several mutagenesis and chimerization studies (Bach *et al.*, 1988; Gottowik *et al.*, 1993; Wu *et al.*, 1993; Chen *et al.*, 1996; Geha *et al.*, 2000), as well as by the crystallization of the two isoenzymes (Binda *et al.*, 2002, 2003; Ma *et al.*, 2004; De Colibus *et al.*, 2005).

Nascent MAO polypeptidic chains undergo a number of posttranslational modifications; the best-characterized processes are the removal of the initiator methionine in MAO-B (but not in MAO-A) and the acetylation of the N-terminus in both molecules (methionine for MAO-A and serine for MAO-B) (Newton-Vinson *et al.*, 2000; Li *et al.*, 2002). Another critical modification is the covalent attachment of FAD to cysteinyl residues 406 in MAO-A and 397 in MAO-B; both amino acids are encoded by exon 12 of the respective gene, and their mutation ablates enzymatic activity (Wu *et al.*, 1993). The coenzyme is attached by a thioether bond with the 8α-methylene group of its isoalloxazine ring (Kearney *et al.*, 1971), and maintained in a position opposite to the entrance of the mono-amine-binding cavity within the active site (Edmondson *et al.*, 2007). The substrate preference and inhibitor specificity appear to be conferred by a number of internal residues, such as Ile 335 in MAO-A and Tyr 326 in MAO-B (Geha *et al.*, 2001).

Both proteins are anchored to the mitochondrial outer membrane through a transmembrane helix located within the carboxyl-terminal domain. In their membrane-bound conformations, human MAO-A and MAO-B are both dimeric (Ma *et al.*, 2004; De Colibus *et al.*, 2005; Binda *et al.*, 2007; Upadhyay *et al.*, 2008; Edmondson *et al.*, 2009).

C. Anatomical Localization of MAO-A and -B

Although both isoenzymes are expressed in most tissues, only MAO-A is characteristically abundant in fibroblasts and placenta; in contrast, MAO-B is the only isoenzyme expressed in platelets and lymphocytes (Bond and Cundall, 1977; Donnelly and Murphy, 1977). MAO-A and -B are present in most brain regions; however, certain areas display only one isoenzyme. MAO-A is found mainly in DAergic and NEergic neurons; conversely, MAO-B is the only isoenzyme expressed in the cell bodies of 5-HTergic neurons (as well as in histaminergic neurons and astrocytes) (Konradi *et al.*, 1989); the significance of this localization remains partially unclear, since 5-HTappears to be mainly metabolized by MAO-A *in vivo*. To account for this apparent mismatch, we have hypothesized that MAO-A protein may be translated in the cell body and segregated to the axon terminals (Bortolato *et al.*, 2010); this hypothesis is supported by the discovery that MAO-B is absent from the mitochondria of the axon terminals (Arai *et al.*, 2002), as well as by the documentation of MAO-A mRNA in the 5-HTergic cells (Luque *et al.*, 1995, 1996; Jahng *et al.*, 1997; Filipenko *et al.*, 2002; Wylie *et al.*, 2010). The proposed compartmentalization may facilitate the specific degradation of 5-HT in the synaptic terminal; further, the expression of MAO-B in the somata of 5-HTergic neurons may serve protective functions for 5-HT.

II. Phenotypical Outcomes of MAO-A Deficit

A. Clinical Findings

The serendipitous discovery of the mood-enhancing effects elicited by MAO pharmacological blockade (Fox and Gibas, 1953) was a historical breakthrough in the pharmacotherapy of mental disorders and gave impetus to the first investigations on the role of MAO in behavioral regulation. It was subsequently discovered that the antidepressant properties of MAO inhibitors were mainly due to the inactivation of MAO-A, which resulted in increased synaptic 5-HT concentrations (Sharp *et al.*, 1997) and modifications of the firing rate of 5-HTergic neurons (Blier and de Montigny, 1985).

The significant side effects of MAO inhibitors, however, led to a progressive decline in the employment of these agents in the therapy of depression, in favor of other categories of antidepressants. The discussion of the antidepressant properties of MAO-A inhibitors and their therapeutic usage is beyond the scope of the present chapter; the interested reader is referred to Amrein *et al.* (1993) and Kennedy (1997).

Interest in the clinical implications of MAO was rekindled by a number of reports on the implications of its deficiency in atypical Norrie disease (ND) patients. This recessive X-linked disease is caused by loss-of-function mutations of *NDP* (Norrie disease pseudoglioma) gene, which encodes for norrin, a protein involved in the development and vascularization of the retina and inner ear. In affected males, total norrin deficiency results in congenital blindness, cataracts, and progressive deterioration of the iris; additionally, several patients experience progressive hearing loss and other abnormalities of the cardiovascular, respiratory, and digestive systems.

As a result of the close proximity of *NDP* (located in Xp11.4) and the two *MAO* genes, a relatively sizable contingent of ND patients are reported to harbor deletion of these genes. In particular, the deletion of *MAO-A* and *MAO-B* in ND patients is conducive to severe mental retardation, growth failure, alterations of sleep pattern, and autistic-like symptoms (Lan *et al.*, 1989a,b; Sims *et al.*, 1989a.b; Murphy *et al.*, 1990; Collins *et al.*, 1992).

Further insight into the phenotypical outcomes of selective MAO-A deficiency was gained with the discovery of a behavioral syndrome in eight males of a large Dutch kindred (Brunner *et al.*, 1993a,b), characterized by borderline mental retardation and maladaptive

regulation of impulsive aggression. The genetic defect was a point mutation in exon 8 of the *MAO-A* gene, resulting in the substitution of a glutamine codon (CAG) with a stop codon (TAG) at position 296 of the amino acid sequence. The main nosographic feature of the disorder was a high proclivity to engage in violent and antisocial behavior (including arson, attempted rape and murder, exhibitionism and voyeurism), often in response to minor stressors. The affected individuals also exhibited stereotyped hand movements and sleep disturbances. These alterations were paralleled by a set of abnormalities in the urinary concentrations of monoamine metabolites, including decreased content of 5-HIAA, HVA, and VMA and increased levels of 5-HT (fivefolds higher than the normal range) and normetanephrine (from COMT metabolism of NE). To the best of our knowledge, no other case of Brunner syndrome has been described in the medical literature to date, even despite specific attempts to identify the disorder in cohorts of aggressive individuals (Mejia *et al.*, 2001).

The sequencing of *MAO-A* gene allowed the characterization of its variants (for a review, see Shih and Thompson, 1999) and their different influence in behavioral regulation; among the numerous allelic variants identified to date, four polymorphisms have been particularly studied as potential biomarkers/risk factors for psychiatric disorders:

1. *MAO-A* (*CA*)n, a dinucleotide repeat polymorphism in intron 2 (Black *et al.*, 1991);
2. a 23 bp variable-number tandem repeat (VNTR) near exon 1 (Hinds *et al.*, 1992);
3. *Fnu*4HI and *Eco*RV, two restriction fragment length polymorphisms (Lim *et al.*, 1994);
4. *MAO-A*-uVNTR, a 30 bp VNTR polymorphism located 1.2 kb upstream of MAO-A transcription initiation site (Sabol *et al.*, 1998).

Variants of the first three polymorphisms (localized in *MAO-A* gene) have been associated to higher susceptibility to several mental conditions; in particular, a robust association was found between bipolar disorder and MAO-A (CA)n and 23 bp-VNTR polymorphisms (Lim *et al.*, 1994, 1995; Kawada *et al.*, 1995; Rubinsztein *et al.*, 1996; Preisig *et al.*, 2000). This association, albeit not confirmed by few studies (Craddock *et al.*, 1995; Muramatsu *et al.*, 1997), was also supported by a meta-analysis study (Furlong *et al.*, 1999).

The *MAO-A*-uVNTR promoter polymorphism has been extensively studied, in consideration of its well-characterized functional nature. Six *MAO-A*-uVNTR variants have been characterized based on a different number of repeats (2, 3, 3.5, 4, 5, and 6) (Huang *et al.*, 2004); in particular, the 3-repeat (3R) and 4-repeat (4R) alleles are the most common in the population (Sabol *et al.*, 1998; Deckert *et al.*, 1999; Jonsson *et al.*, 2000); of these, the 4R variant has been associated to higher transcriptional efficiency and enzymatic activity (Sabol *et al.*, 1998; Deckert *et al.*, 1999; Denney *et al.*, 1999). In line with this finding, a number of studies have shown that 4R carriers have higher levels of 5-HIAA in the cerebrospinal fluid (Williams *et al.*, 2003), as well as a higher prevalence of panic disorder and major depression (in females), with poor response to chronic fluoxetine treatment (Deckert *et al.*, 1999; Yu *et al.*, 2005).

The 3R variant, which has been found to result in lower MAO-A catalytic activity in fibroblasts, has been linked to a higher risk for behavioral traits related to Brunner syndrome symptoms, namely impulsive aggressiveness and antisocial personality (Samochowiec *et al.*, 1999; Contini *et al.*, 2006; Oreland *et al.*, 2007; Buckholtz and Meyer-Lindenberg, 2008; Williams *et al.*, 2009), as well as impaired stress response (Brummett *et al.*, 2008), lower cognitive functioning (Cohen *et al.*, 2003), and maladaptive emotional processing of affect (Lee and Ham, 2008). Interestingly, this variant has also been shown to influence the clinical

course and severity of mental disorders; for example, 3R autistic children exhibit higher severity of the pathological manifestations (Cohen *et al.*, 2003), lower levels of anxiety and attentional deficits (Roohi *et al.*, 2009), and larger cortical volumes (Davis *et al.*, 2008).

The behavioral changes associated to *MAO-A*-uVNTR polymorphic variants have been documented to be related to a number of morphological and functional differences between the brains of 3R and 4R carriers. In particular, several studies have shown that male individuals with the 3R haplotype exhibit morphological alterations of the orbitofrontal cortex (Meyer-Lindenberg *et al.*, 2006; Cerasa *et al.*, 2008, 2010), as well as functional abnormalities in several cortical and limbic regions, including prefrontal cortex, amygdala, and hippocampus (Meyer-Lindenberg *et al.*, 2006; Passamonti *et al.*, 2006).

Recent findings have challenged the association between *MAO-A*-uVNTR variants and MAO-A brain activity. For example, postmortem studies showed that, while the average MAO-A catalytic activity in brain samples from 4R carriers was higher than 3R, this difference was not significant (Balciuniene *et al.*, 2002). Similarly, investigations conducted on populations of 3R and 4R male carriers with positron emission tomography [PET] for [^{11}C]clorgyline revealed no significant difference in brain MAO-A activity between the two groups (Fowler *et al.*, 2007; Alia-Klein *et al.*, 2008). However, irrespective of the genetic components, MAO-A activity in cortical and subcortical brain regions was shown to be inversely correlated with the degree of self-reported aggression in men (Alia-Klein *et al.*, 2008).

These data strongly suggest that polymorphic variants, rather than dictating MAO-A activity, may only confer a predisposition to a higher or lower baseline level of this index. Indeed, a large number of environmental factors have been shown to modify MAO-A expression and activity, including stress (Maura and Vaccari, 1975), diet changes (Jahng *et al.*, 1998), tobacco smoking (Fowler *et al.*, 1996), physical exercise (Morishima *et al.*, 2006), social environment (Filipenko *et al.*, 2002), and aging itself (Saura *et al.*, 1994). Thus, the interaction between a genetic predisposition and specific environmental determinants could induce variations of MAO-A activity and increase the vulnerability to develop aggressive conduct and antisocial personality.

In line with this possibility, Caspi and coworkers reported that male 3R-carriers with a history of abuse during childhood had a significantly higher prevalence of aggressive behavior in adulthood than 3R-carriers with no history of early maltreatment or 4R-carriers with history of abuse (Caspi *et al.*, 2002). This important finding has been confirmed by subsequent studies (Foley *et al.*, 2004; Huang *et al.*, 2004; Kim-Cohen *et al.*, 2006; Edwards *et al.*, 2010). Further, recent evidence shows that the effects of early stress on impulsivity are reduced by high levels of perceived parental care in individuals with the 3R-, but not the 4R, allelic variant (Kinnally *et al.*, 2009). These results highlight the importance of gene × environment interactions in the pathophysiology of the conditions associated with low MAO-A activity.

B. Preclinical Findings

The analysis of the psychopathological implications of MAO-A deficiency and their neurobiological underpinnings is greatly limited by the rarity of Brunner syndrome and its elusive nosographic description (Hebebrand and Klug, 1995; Schuback *et al.*, 1999). A useful experimental tool to partially obviate this limitation has been afforded by MAO-A knockout (KO) mice. The first line of these mutants was generated in the C3H/HeJ strain by the insertion of an interferon-β minigene into exon 2 of *Maoa* gene (Cases *et al.*, 1995). More recently, another murine line has been developed in 129S6 background, carrying a spontaneous nonsense point mutation of the exon 8 (in a position close to that documented

in Brunner syndrome patients) (Scott *et al.*, 2008). Although strain differences may play a modulatory role in phenotypical manifestations, our results have shown that the neurochemical and behavioral phenotypes of both lines bear striking resemblances (Scott *et al.*, 2008).

The selective loss of MAO-A enzymatic function leads to high levels of brain 5-HT and NE, as well as a broad spectrum of phenotypical aberrances, highly reminiscent of the symptoms described in Brunner syndrome. The most evident behavioral alteration in MAO-A KO mice consists in their elevated aggressiveness, toward both foreign mice and cage mates (Cases *et al.*, 1995; Scott *et al.*, 2008). Further, MAO-A KO mice display marked reduction in exploratory activity (Godar *et al.*, 2011), low levels of depression-like behavior in the forced swim test (Cases *et al.*, 1995) and high level of mnemonic retention of aversive events (Kim *et al.*, 1997; Dubrovina *et al.*, 2006).

Recent studies in our laboratory have begun to elucidate the potential psychopathological bases of the emotional alterations in MAO-A KO mice. In particular, we have observed that these mutants exhibit maladaptive defensive reactivity to different contextual cues. In particular, MAO-A KO mice display high levels of neophobia and antagonistic behavior in presence of novel neutral objects (particularly if introduced within a familiar context); conversely, they increase their level of exploration (with no aggressive or defensive postures) in the presence of cues associated with high danger, such as objects impregnated with predator urine or an anesthetized rat.

In line with this background, MAO-A deficient mice display exaggerated freezing reactions to relatively minor stressors (such as a mild footshock) (Kim *et al.*, 1997), but reduced endocrine responses to major environmental stress, such as physical restraint, water deprivation, cold temperature, and chronic variable stress (Popova *et al.*, 2006).

In conflict-based models of anxiety (which are based on the contrast of exploratory drive and neophobia), MAO-A KO mice did not display major behavioral alterations associated with anxiety-like behavior, but did show a reduction in risk-assessment postures (Popova *et al.*, 2001; Godar *et al.*, 2011). This phenomenon may be partially explained by the simultaneous decrease in avoidance/fear-related behaviors as well as approach/exploration in most contextual settings (Godar *et al.*, 2011).

Taken together, these studies suggest that most behavioral alterations featured in MAO-A KO mice may depend on their inability to attune their responses to environmental inputs. In particular, their maladaptive responses are similar to the deficits in facial affect processing in schizophrenia and autism patients (Phillips *et al.*, 1999; Bolte and Poustka, 2003; Dawson *et al.*, 2004; Surguladze *et al.*, 2006; Gur *et al.*, 2007; Hall *et al.*, 2008).

Although the assessment of the morphological characteristics in the brain of MAO-A KO mice is still incomplete, the most remarkable feature identified to date is the dysmorphogenesis of the barrel fields in layer IV of the somatosensory cortex (Cases *et al.*, 1995). Barrel fields are the cortical representations of the mystacial vibrissae in the rodent snout, and their formation depends on the thalamocortical projections arising from ventrobasal thalamic nuclei (Erzurumlu and Jhaveri, 1990).

The impairment of barrel fields has been associated with alterations of perceptual processing, exploratory activity, and sensory integration (Hurwitz *et al.*, 1990; Sanders *et al.*, 2001; Dowman and Ben-Avraham, 2008; Straube *et al.*, 2009), suggesting similar deficits in MAO-A KO mice. Nevertheless, we showed that these animals were able to recognize familiar objects both in the presence or absence of environmental light in a fashion comparable with their wild-type (WT) littermates (Godar *et al.*, 2011). This finding

challenges the possibility that the behavioral alterations observed in MAO-A KO mice may be strictly reflective of their deficits in vibrissal function.

The analysis of sensory modalities in both MAO-A KO lines has revealed impairments in acoustic reactivity (Cases *et al.*, 1995), in line with defects in the auditory pathways (Thompson, 2008; Thompson and Thompson, 2009). Although MAO-A deficiency may also result in subtle developmental alterations of retinal projections (Upton *et al.*, 1999), these deficits do not seem to affect the visual acuity of the mice, as assessed with the visual cliff paradigm (Godar *et al.*, 2011). Similarly, MAO-A KO mice do not exhibit any overt change in olfactory discrimination (Godar *et al.*, 2011).

Previous studies have shown that long-term treatment with MAO-A inhibitors in adult rodents induces a decrease in defensive behavior against predators (Griebel *et al.*, 1998), and an enhancement in exploratory activity (Steckler *et al.*, 2001). These alterations are distinctly different from those observed in MAO-A KO mice, highlighting the likely contribution of early developmental mechanisms in the alterations associated with MAO-A deficiency. Accordingly, early treatment with clorgyline and other MAO inhibitors was found to induce behavioral alterations and impairments in thalamocortical development similar to those observed in MAO-A KO mice (Whitaker-Azmitia *et al.*, 1994; Boylan *et al.*, 2000; Mejia *et al.*, 2002). Moreover, the neurobehavioral alterations of MAO-A KO mice begin at very early stages, with intense head bobbing, prolonged righting, and trembling and delayed maturation of motor skills (Cases *et al.*, 1995; Cazalets *et al.*, 2000). In addition, MAO-A KO mice feature abnormalities of respiratory activity (Bou-Flores *et al.*, 2000). Between postnatal days 11 and 16, MAO-A KO mice display hyperlocomotion, jumping, abnormal postures, and hyperreactivity to stimuli (Cases *et al.*, 1995).

Several studies have shown that the sensorimotor cortex deficits in these animals are due to neurodevelopmental alterations based on the excessive 5-HT levels and 5-HT1B receptor hyperactivation in the first days of postnatal life (Cases *et al.*, 1995; Vitalis *et al.*, 1998; Salichon *et al.*, 2001). In contrast, the morphological alterations of the respiratory centers in the medulla and the cervical phrenic motoneurons in MAO-A KO are reversed by 5-HT2A receptor inhibition (Bou-Flores *et al.*, 2000).

III. Phenotypical Outcomes of MAO-B Deficit

A. Clinical Findings

Although the functional role of MAO-B in brain and behavioral regulation is more elusive than MAO-A, numerous lines of evidence point to its role in emotional regulation. The main MAO-B substrate, PEA, is widely regarded as an endogenous amphetamine, in view of its similar chemical structure and effects *in vivo*, which include increased alertness, euphoria, insomnia, and tremor (Baud *et al.*, 1985; Zucchi *et al.*, 2006). In line with this concept, numerous studies have highlighted a key role of this trace amine in the pathophysiology of schizophrenia and other neuropsychiatric disorders (Beckmann *et al.*, 1983; Szymanski *et al.*, 1987; O'Reilly *et al.*, 1991; Berry, 2007).

Alterations of MAO-B activity and expression have been associated with a broad constellation of neuropsychiatric manifestations, including psychotic disorders, depression, alcoholism, impulsivity, and neurodegenerative diseases (Mann and Chiu, 1978; Adolfsson *et al.*, 1980; Sandler *et al.*, 1993). In addition to its well-characterized neuroprotective role in PD therapy, the prototypical MAO-B inhibitor selegiline has been shown to exert mood-enhancing and anxiolytic effects in depression (Mendlewicz and Youdim, 1983; Quitkin *et al.*, 1984; Robinson *et al.*, 2007) and other pathological conditions (Tariot *et al.*, 1987; Tolbert and Fuller, 1996).

Most clinical studies on MAO-B function have focused on the activity of this enzyme in platelets, as these bodies can be easily collected and display exclusively this isoenzyme. Other advantages of this index lie in its high heritability (Oxenstierna *et al.*, 1986; Pedersen *et al.*, 1993), as well as in its potential association to brain MAO-B catalytic activity (af. Klintenberg *et al.*, 2004). Rich evidence shows a robust correlation between low MAO-B platelet activity and a spectrum of psychological traits related to behavioral disinhibition, such as sensation-seeking and novelty-seeking personality, extraversion, poor impulse control, and proclivity to engage in risky behaviors (Buchsbaum *et al.,* 1976; Fowler *et al.*, 1980; von Knorring *et al.,* 1984; Reist *et al.*, 1990; for a review, see Oreland and Hallman, 1995). While the discovery that smoking can reduce MAO-B activity (Simpson *et al.*, 1999; Hauptmann and Shih, 2001) partially tempered this notion, in view of the high prevalence of this habit among sensation-seekers, further studies confirmed that the association between low MAO-B activity and novelty-seeking remain even after controlling for this environmental factor (Ruchkin *et al.*, 2005).

To the best of our knowledge, there have been no reports of clinical conditions characterized by selective MAO-B deficiency. However, in few cases of atypical ND with MAO-B deletion, the latter deficit was reported to result in increased urinary excretion of PEA, but no overt behavioral abnormalities or cognitive deficits (Berger *et al.*, 1992; Lenders *et al.,* 1996).

Several MAO-B polymorphic variants have been significantly associated with a number of psychological traits, such as negative emotionality (Dlugos *et al.*, 2009), and neuropsychiatric conditions, such as attention-deficit hyperactivity disorder (Li *et al.*, 2008; Ribasés *et al.*, 2009). This association is particularly intriguing, as other authors have documented associations between low platelet MAO-B activity with attention-deficit hyperactivity (Shekim *et al.*, 1986; Coccini *et al.*, 2009; Nedic *et al.*, 2010). Notably, sensation-seeking personality and poor impulse control are key features of ADHD psychopathology.

One of the best-characterized functional MAO-B polymorphisms consists in a single-base variation (A or G) in the intron 13 (Kurth *et al.*, 1993); the A allele has been associated with lower MAO-B catalytic activity in platelets (Garpenstrand *et al.*, 2000) and higher activity in the brain (Balciuniene *et al.*, 2002). However, other studies have failed to detect any connection between this polymorphism and the enzymatic activity (Girmen *et al.*, 1992).

An increase in MAO-B activity and/or expression has been associated with PD; accordingly, few studies have revealed associations between MAO-B polymorphisms and specific clusters of this disease (Kang *et al.*, 2006; Bialecka *et al.*, 2007). Nevertheless, the results on the potential connection between the polymorphism of intron 13 and PD remain controversial (Kurth *et al.*, 1993; Ho *et al.*, 1995; Costa *et al.*, 1997).

B. Preclinical Findings

A complementary line of evidence on the phenotypical implications of MAO-B deficits has been provided by the generation of MAO-B KO mice (Grimsby *et al.*, 1997), achieved by targeted insertion of a foreign neomycin resistance cassette in exon 6 of *Maob* gene. In this line of mice, the lack of MAO-B catalytic activity resulted in significantly higher levels of PEA in brain. However, levels of major monoamine neurotransmitters (5-HT, NE, and DA) were comparable with those in WT mice.

The initial studies aimed at the behavioral characterization of MAO-B KO mice did not highlight many overt behavioral and cognitive changes. For example, unlike MAO-A-deficient animals, MAO-B KO mice display no significant alteration of aggressive behavior.

The most remarkable alterations were a reduced level of immobility in the forced swim test (Grimsby *et al.*, 1997). This phenomenon was originally interpreted as an enhancement in stress responsiveness; however, recent studies have shown that MAO-B KO mice display low levels of restraint-induced hyperthermia, a typical parameter of stress reactivity (Bortolato *et al.*, 2009). Taken together, these data suggest that the behavioral performance in MAO-B KO mice was likely reflective of their increased ability to counteract the stress induced by hazardous situations.

We recently documented that MAO-B KO mice display responses reminiscent of behavioral disinhibition, increased novelty-seeking, and reduced anxiety in a number of complementary behavioral paradigms aimed at capturing different aspects of emotional reactivity. For example, MAO-B KO mice displayed significant reduction in anxiety-like behaviors in an elevated plus maze, as well as in the defensive withdrawal, marble burying, hole-board. In addition, MAO-B KO mice displayed a high inclination to explore unfamiliar objects and displayed low novelty-induced grooming, suggesting an enhancement of novelty-seeking behavior (or reduction of neophobia) in these animals. These results are in agreement with the numerous findings on the correlation between low MAO-B platelet activity and novelty-seeking personality, and point to a causal link between the two phenomena.

Interestingly, the abnormal characteristics of MAO-B KO mice were best observed in the presence of several environmental adjustments, such as the reduction of environmental light, a strong anxiogenic factor in mice. This consideration suggests that the ablation of MAO-B may result in variations of personality, rather than actual pathological outcomes.

However, it is extremely likely that low MAO-B activity may be a key vulnerability factor for several conditions associated with sensation-seeking conduct. Future studies will have to evaluate what factors (both genetic and environmental) can interact with low MAO-B activity to induce pathological outcomes.

PEA has been implicated in the regulation of emotional responses, including exploratory activity, arousal, and behavioral reinforcement (Sabelli and Javaid, 1995). MAO-B KO mice display high levels of this monoamine particularly in striatum. Given the implication of PEA in the regulation of DA functions (Kuroki *et al.,* 1990; Sotnikova *et al.,* 2004) and the relevance of DA in behavioral disinhibition (Megens *et al.,* 1992; Black *et al.,* 2002; van Gaalen *et al.,* 2006) and anxiolysis (Shabanov *et al.,* 2005; Picazo *et al.,* 2009), it is possible that DA may play an important role in the behavioral features of MAO-B KO mice. In line with this possibility, MAO-B KO mice have been shown to feature hypersensitivity of D1 receptor (Chen *et al.*, 1999), which have been implicated in the motivational aspects of novelty-seeking behavior (Peters *et al.*, 2007; Olsen and Winder, 2009).

IV. Phenotypical Outcomes of Combined MAO-A and MAO-B Deficit

A. Clinical Findings

As outlined above, the phenotypical outcomes of joint MAO-A and MAO-B deficiency could be initially surmised by comparisons between atypical ND patients with deletion of both genes and their counterparts with mutations restricted to *NDP* gene. These studies suggested that total congenital MAO deficit resulted in a spectrum of severe developmental deficits, with profound mental retardation and autistic-like behavior (Sims *et al.*, 1989a,b; Murphy *et al.*, 1990; Collins *et al.*, 1992). The ultimate description of the consequences of total MAO deficiency, however, was recently provided by Whibley and colleagues, who reported the case of two male siblings carrying a 240 kb deletion in Xp11.3, which encompassed exons 2–15 of *MAO-A* and all exons of *MAO-B*, but no mutations of NDP or other adjacent genes (Whibley *et al.*, 2010).

The two affected children were born to healthy, nonconsanguineous Caucasian parents and presented with a spectrum of severe abnormalities, including major developmental delay (with height and weight on very low percentiles), mental retardation, and stereotypical movements (hand-flapping and lip-smacking) akin to those featured in Rett syndrome and other pervasive developmental disorders (Whibley *et al.*, 2010). Both brothers had exhibited several episodes of profound hypotonia since perinatal stages, which was typically resistant to phenobarbital, sodium valproate, and lamotrigine. One patient, who displayed minor dysmorphic features (inner canthal folds and an extra incisor) and EEG alterations, died at 5 years of age. His autopsy revealed small foci of perivascular calcification with loss of Purkinje cells in the cerebellum and neurons in the cortex (Whibley *et al.*, 2010).

B. Preclinical Findings

Following the fortuitous discovery of a mouse with a spontaneous mutation in *Maoa* gene within the MAO-B KO colony (Chen *et al.*, 2004), a colony of MAO-A/B KO mice was established, and their phenotypes were characterized. The lack of catalytic activity for either MAO isoenzymes was confirmed by a high increase in brain levels of all monoamines (5-HT: 850%; NE: 220%; DA: 170%; PEA: 1570%) in comparison to WT littermates. Interestingly, the magnitude of these enhancements is significantly greater than those observed in either MAO-A or MAO-B KO mice, suggesting that, in the absence of one isoenzyme, the other can partially overtake its catalytic role. This concept underscores that the alterations induced by joint MAO-A and MAO-B deficiency do not simply result from the summation of the aberrant phenotypes related to each mutation. In fact, it is likely that the abnormalities exhibited by MAO-A/B KO mice may be largely mediated by the exposure to extremely high concentrations of monoamines (in particular 5-HT) in early developmental stages. Preliminary phenotypical analyses of MAO-A/B KO mice revealed that these animals display major developmental alterations (not observed in either MAO-A or MAO-B KO mice), with weight and size at birth significantly lower than WT littermates. These animals also exhibit a complex array of behavioral abnormalities, including aberrant emotional response to novelty, high levels of anxiety-like behaviors in select tasks and low latency to attack in the resident-intruder paradigm (Chen *et al.*, 2004). Recent studies conducted in our laboratory suggest that MAO-A/B KO mice may display alterations in emotional reactivity and informational processing similar (but more severe) to those observed in MAO-A KO mice (unpublished observations). In contrast, these mutants show no patent analogies with the behavioral changes of MAO-B KO mice, likely due to the phenotypical predominance of the defects associated with MAO-A deficiency.

V. Conclusions

Since the cloning of *MAO-A* and *MAO-B* genes in 1988, the employment of complementary approaches has paved the way for the elucidation of the structural and functional characteristics of these two genes and their products. Over the past few years, the advances in the analysis of the phenotypical variations associated with the polymorphisms of both genes has revealed a number of promising leads for the understanding of their role in mental illness and behavioral regulation. Novel findings in the phenotypes of MAO-deficient mice are highlighting novel potential implications of both isoenzymes in a broad spectrum of mental disorders, ranging from autism and anxiety to impulse-control disorders and ADHD. These studies will lay the foundation for future research on the neurobiological and neurochemical bases of these pathological conditions, as well as the role of gene × environment interactions in the vulnerability to several mental disorders.

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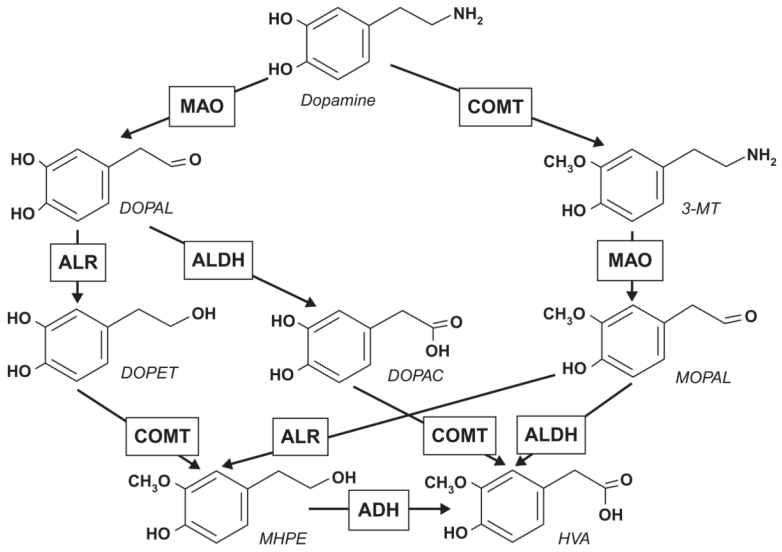


Fig. 1.

Metabolic pathways of dopamine. DOPAL, 3,4-dihydroxyphenylacetaldehyde; 3-MT, 3-methoxytyramine; DOPET, 3,4-dihydroxyphenylethanol; DOPAC, 3,4-dihydroxyphenylacetic acid; MOPAL, 3-methoxy-4-hydroxyphenylacetaldehyde; MHPE, 3-methoxy-4-hydroxyphenylethanol; HVA, homovanillic acid.

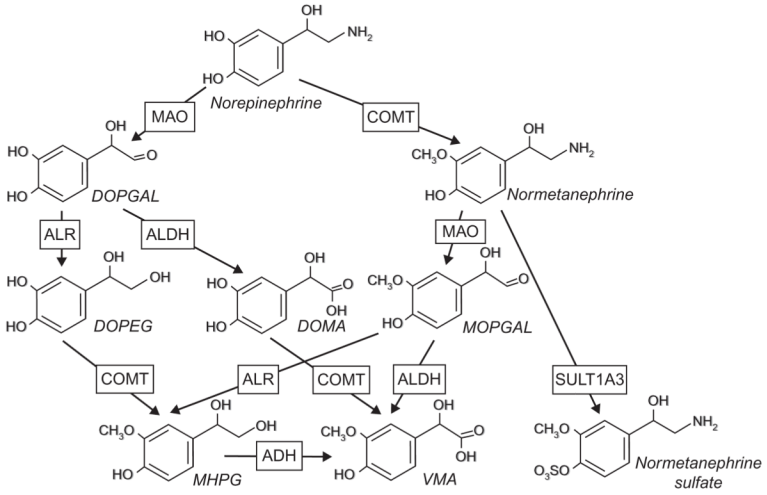
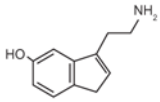
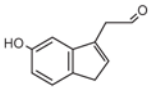
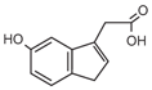
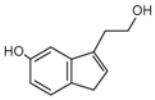
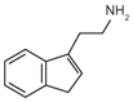
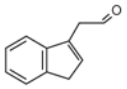
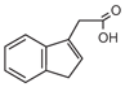
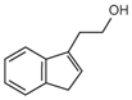
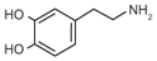
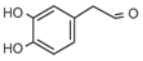
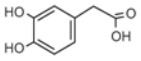
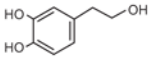
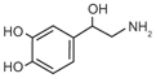
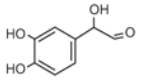
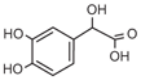
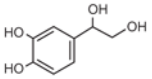
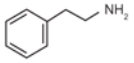
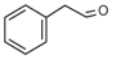
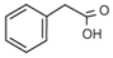
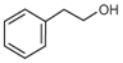
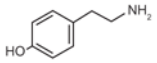
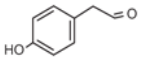
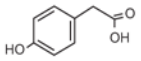
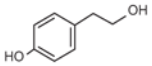


Fig. 2.

Metabolic pathways of norepinephrine. DOPGAL, 3,4-dihydroxyphenylglycol aldehyde; DOPEG, 3,4-dihydroxylphenylethylene glycol; DOMA, 3,4-dihydroxymandelic acid; MOPGAL, 3-methoxy-4-hydroxyphenylglycol aldehyde; MHPG, 3-methoxy-4-hydroxyphenylethylene glycol; VMA, vanillyl mandelic acid.

Table I

Synoptic View of the Main Substrates and Products of MAO-Mediated Metabolism (Coupled with Aldehyde Dehydrogenase (ALDH) or Aldehyde Reductase (ALR)).

Substrates		Products		
		MAO	ALDH	ALR
Indolamines	 Serotonin	 5-HIAAL	 5-HIAA	 5-HIET
	 Tryptamine	 IAAL	 IAA	 IET
Cathecolamines	 Dopamine	 DOPAL	 DOPAC	 DOPET
	 Norepinephrine	 DOPGAL	 DOMA	 DOPEG
Other trace amines	 PEA	 PAAL	 PAA	 PET
	 Tyramine	 HPAL	 HPA	 HPET

Epinephrine is not listed, as its metabolites are the same as those indicated for norepinephrine.

Abbreviations: 5-HIAAL, 5-hydroxyindolaldehyde; 5-HIAA, 5-hydroxyindolacetic acid; 5-HIET, 5-hydroxyindolethanol; IAAL, indole-3-acetaldehyde; IAA, indole-3-acetic acid, IET, indole-3-ethanol (tryptophol); DOPAL, 3,4-dihydroxyphenylacetaldehyde; DOPAC, 3,4-dihydroxyphenylacetic acid; DOPET, 3,4-dihydroxyphenylethanol; DOPGAL, 3,4-dihydroxyphenylglycolaldehyde; DOMA, 3,4-dihydroxymandelic acid; DOPEG, 3,4-dihydroxylphenylethyleneglycol; PEA, 2-phenylethylamine; PAAL, 2-phenylacetaldehyde; PAA, 2-phenylacetic acid; PET, 2-phenylethanol; HPAL, 4-hydroxy-phenylaldehyde; HPA, 4-hydroxyphenylacetic acid; HPET, 4-hydroxyphenylethanol.