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From aggression to autism: new perspectives on the behavioral sequelae of monoamine oxidase deficiency

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Abstract

The two monoamine oxidase (MAO) enzymes, A and B, catalyze the metabolism of monoamine neurotransmitters, such as serotonin, norepinephrine, and dopamine. The phenotypic outcomes of MAO congenital deficiency have been studied in humans and animal models, to explore the role of these enzymes in behavioral regulation. The clinical condition caused by *MAOA* deficiency, Brunner syndrome, was first described as a disorder characterized by overt antisocial and aggressive conduct. Building on this discovery, subsequent studies were focused on the characterization of the role of *MAOA* in the neurobiology of antisocial conduct. MAO A knockout mice were found to display high levels of intermale aggression; however, further analyses of these mutants unveiled additional behavioral abnormalities mimicking the core symptoms of autism-spectrum disorder. These findings were strikingly confirmed in newly-reported cases of Brunner syndrome. The role of *MAOB* in behavioral regulation remains less well-understood, even though *Maob*-deficient mice have been found to exhibit greater behavioral disinhibition and risk-taking responses, supporting previous clinical studies showing associations between low MAO B activity and impulsivity. Furthermore, lack of *MAOB* was found to exacerbate the severity of psychopathological deficits induced by concurrent *MAOA* deficiency. Here, we summarize how the convergence of clinical reports and behavioral phenotyping in mutant mice has helped frame a complex picture of psychopathological changes in MAO-deficient individuals, which encompass a broad spectrum of neurodevelopmental problems. This emerging knowledge poses novel conceptual challenges towards the identification of the endophenotypes shared by autism-spectrum disorder, antisocial behavior and impulse-control problems, as well as their monoaminergic underpinnings.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

Monoamine oxidase; Brunner syndrome; aggression; impulse control; autism; behavior; animal models

Introduction: function and distribution of monoamine oxidases (MAOs)

MAOs are mitochondrial membrane-bound flavoproteins that catalyze the oxidative deamination of neurotransmitters, as well as biogenic and xenobiotic amines (Edmondson et al., 2004), to the corresponding aldehydes:

$$RCH_2NHR' + H_2O + O_2 \rightarrow RCHO + R'NH_2 + H_2O_2$$

This reaction requires flavin adenine dinucleotide (FAD) as a covalently bound redox cofactor. The reduction of FAD to its hydroquinone form ($FADH_2$) enables the conversion of a primary amine substrate into the corresponding imine, which is then spontaneously hydrolyzed to an aldehyde and ammonia. The overall reaction is completed by the re-oxidation of MAO-attached $FADH_2$ into FAD, which leads to the formation of hydrogen peroxide from oxygen (Pizzinat et al., 1999).

The reaction catalyzed by MAOs is instrumental in reducing the potential cardiotoxicity and neurotoxicity of xenobiotic and endogenous amines; however, its products -aldehydes, ammonia and hydrogen peroxide, are also extremely toxic, and need to undergo further metabolic processing to avoid cell damages. In the CNS, the carbonyl groups of the aldehydes produced by MAOs are typically oxidized by mitochondrial aldehyde dehydrogenase (ALDH-2) (Tank et al., 1981; Ambroziak and Pietruszko, 1991), resulting into the formation of carboxylic acids, which are then rapidly conveyed to the bloodstream and excreted by the kidneys. It should be noted, however, that small amounts of aldehydes can undergo processing by aldehyde reduction (ALR), particularly in peripheral tissues, leading to the formation of alcohols (Feldstein and Williamson, 1961; for additional details, see Bortolato et al., 2011). The detoxification of ammonia in the brain largely relies on glutamine synthesis in the astrocytes (by glutamine synthetase) (Suarez et al. 2002; Rose et al. 2013). Finally, hydrogen peroxide is also converted into water and molecular oxygen by catalase (Jones and Suggett, 1968); alternatively, however, it can lead to the formation of reactive oxygen species. Taken together, this background illustrates that the function of MAOs in the CNS is enabled by a complex detoxification machinery in the CNS; furthermore, it may help explain the beneficial effects of MAO inhibitors in neurodegenerative problems.

While only one MAO is found in invertebrates and fish (Boutet et al., 2004; Setini et al., 2005; Anichtchik et al., 2006), tetrapods have two isoenzymes, A and B, encoded by two adjacent X-linked genes (Bach et al., 1988; Lan et al., 1989) with the same sequence of exons and introns (Grimsby et al., 1991), likely resulting from the tandem duplication of a common ancestral gene (Grimsby et al., 1991). MAO A and B share a high homology (~70%) and similar intracellular location and structural characteristics (both enzymes are

homodimeric in their membrane-bound forms). Despite these common features, MAO A and B differ by molecular weight, anatomical distribution, developmental ontogeny, substrate affinity, pharmacological responsiveness to inhibitors, and functional role. MAO A preferentially oxidizes serotonin (5-HT) and norepinephrine (NE), while MAO B displays the highest affinity for the trace amine β-phenylethylamine (PEA) (Bortolato et al., 2008). Dopamine (DA) is catabolized by both isoenzymes, with different levels of affinity depending on the species: it is primarily a MAO A substrate in rodents and a MAO B substrate in humans and other primates (Glover et al., 1977; Bortolato et al. 2008). Despite this physiological divergency, each MAO isoenzyme contributes to the metabolism of non-preferred substrates in the absence of the other enzyme.

MAO A and B are also differentially expressed across different tissues and developmental periods: MAO A, for example, is highly abundant in placenta, where it serves a protective role for the fetus; in addition, this enzyme is found in fibroblasts and several peripheral organs, including liver, lung, small intestine; in contrast, its expression is scarce in the spleen and brain microvessels and absent in platelets and lymphocytes (Bond and Cundall, 1977; Donnelly and Murphy, 1977). MAO B is highly expressed in the intestine and liver and is the only MAO enzyme expressed in platelets and lymphocytes; however, this enzyme is either absent or poorly represented in the placenta, pancreas, spleen, lung and skin fibroblasts (Dahlstrom and Fuxe, 1964; Grimsby et al., 1990). Both MAOs are expressed in the brain: MAO B is predominant in serotonergic and histaminergic neurons (Jahng et al., 1997; Kitahama et al., 1991; Luque et al., 1995), as well as in glial cells (Ekblom et al., 1993; Nakamura et al., 1990), while MAO A is primarily found in catecholaminergic cells. The functional significance of these different distributions is not yet fully understood.

The developmental ontogeny of MAO A and B also follows differential trajectories. In most species, it appears that MAO A activity is predominant in early organogenesis; conversely, MAO B is not detectable in perinatal stages, but tends to increase with aging (Nicotra et al., 2004). Indeed, MAO B is one of the few enzymes the expression and activity of which is enhanced by aging, raising the important issue whether its activity may contribute to some degenerative processes, possibly through the production of H_2O_2. Accordingly, research has shown high brain MAO B levels in neurodegenerative diseases, such as Parkinson’s and Alzheimer’s diseases (Saura et al., 1994; Jossan et al., 1991); further, MAO B inhibitors have been shown to improve the quality of life in elderly (Knoll, 1993). Further knowledge of the time-courses of MAO isoenzyme expression in different tissues will be important to our understanding of the developmental roles of the monoamine neurotransmitters.

Although the chemical functions of MAOs are well-known, the contributions played by these enzymes in the regulation of brain functions have only been partially elucidated. Over the past two decades, however, significant progress has been made on our understanding of the behavioral processes affected by MAOs. Clinical research on genetic variants of both MAOA and MAOB, as well as preclinical investigations in mutant mouse models have been particularly instrumental to advance our understanding the understand the mechanisms by which these enzymes can affect behavioral responses. In the next sections, we will summarize the current knowledge on the role of MAOA and MAOB in behavioral regulation, with a particular emphasis on the phenotypic conditions resulting from loss-of-

function mutations of either gene. We will also underscore how discoveries in mutant mice were particularly instrumental in driving recent ideas on the diagnosis, pathophysiology and therapy of these conditions.

Neurobehavioral outcomes of *MAOA* deficiency: Brunner syndrome

The first finding that spurred significant attention on the role of MAO A in behavioral organization was the discovery of a selective *MAOA* congenital deficiency in 14 males from a large Dutch kindred by Brunner and colleagues (Brunner et al., 1993a; 1993b). Genetic analyses revealed a point mutation in exon 8, which led to the substitution of a glutamine codon with a stop codon. The subjects affected by Brunner syndrome were characterized by episodic impulsive aggression, which had resulted in the perpetration of various criminal acts, including attempted rape and murder, as well as arson, voyeurism and exhibitionism (Brunner et al., 1993a; 1993b). Strikingly, these violent outbursts were typically enacted in response to bereavement or minor provocations, raising the possibility that *MAOA* deficiency may lead to antisocial and violent conduct as a maladaptive response to environmental triggers. Importantly, Brunner syndrome patients were also reported to exhibit mild cognitive impairments, as well as stereotyped hand movements and parasomnias. These deficits were associated with aberrances of the urinary composition, including a dramatic reduction in 5-hydroxyindolacetic acid (5-HIAA, the main metabolite of serotonin), HVA (homovanillic acid) and VMA (vanillylmandelic acid), as well as an increase in serotonin content. Heterozygous female carriers of the mutation did not show any overt psychopathological outcomes, suggesting that 50% expression of the enzyme is sufficient to afford regular behavioral functioning.

The fact that all Brunner syndrome patients came from the same family raised doubts about the generalizability of these findings; unfortunately, the search for other cases of *MAOA* deficiency proved unfruitful for the next two decades, and no samples were found in populations of aggressive individuals (Murphy et al., 1998; Schuback et al., 1999; Meija et al., 2001). This stall notwithstanding, significant advances on the phenotype of *MAOA* deficiency were made thanks to the development of mouse transgenic lines carrying loss-of-function mutations of *Maoa* gene. The first line of knockout (KO) mice was generated by insertion of an interferon beta cassette into exon 2 of this gene (Cases et al., 1995). Another line of mutants, this time featuring a spontaneous point mutation in exon 8, was later reported by our group (Scott et al., 2008). Irrespective of the specific sites of mutation and different background strains (C3H/HeJ and 129S6), both lines have been shown to feature very similar behavioral and biochemical profiles (Scott et al., 2008). The first analyses in MAO A KO mice were focused on their most obvious behavioral abnormality, namely an overt increase in aggression towards familiar and unfamiliar social counterparts (Cases et al., 1995; Scott et al., 2008). A more refined level of scrutiny, however, revealed that aggressive responses in MAO A KO mice were only one of the behavioral epiphenomena of *Maoa* deficiency. Our work was particularly aimed at identifying the endophenotypic alterations underlying these behavioral changes. We initially characterized that the reactivity of MAO A KO mice was influenced by environmental stimuli in a bimodal fashion that typically differed from that of wild-type (WT) littermates. Specifically, MAO A KO mice were found to display fewer anxiety-like behaviors and more exploratory drive in contingencies that

were associated with predator cues; conversely, they exhibited significant reductions in their inclination to explore novel environments, even under conditions that attenuated neophobia in their WT counterparts (Godar et al., 2011). By the same token, environmental familiarization did not reduce neophobia, but paradoxically increased antagonistic and defensive responses in MAO A KO mice (Godar et al., 2011). Similar maladaptive reactions were observed with respect to stress: for example, MAO A KO mice exhibited exaggerated freezing to relatively minor stressors (Kim et al., 1997), but lower endocrine, behavioral and cellular responses to physical restraint and other highly stressful manipulations (Popova et al., 2006; Godar et al., 2015).

We later identified that this maladaptive reactivity was contributed by deficits in information processing by the prefrontal cortex. Functional deficits of this region have been widely shown to impair the ability to interpret and adapt to environmental information (Arnsten, 2009). Our studies showed that NMDA glutamate receptors in the prefrontal cortex of MAO A KO mice display alterations in their subunit composition, leading to a general reduction in channel conductance (Bortolato et al., 2012). This impairment is likely conducive to lower excitability of prefrontal neurons, and may result in connectivity deficits. Accordingly, we also found that MAO A KO mice displayed alterations of the apical and basilar dendritic arbor of pyramidal cells in the prefrontal cortex (Bortolato et al., 2013a).

Our subsequent analyses disclosed that the behavioral repertoire of MAO A KO mice reproduced all major core deficits observed in autism-spectrum disorder (ASD), including social deficits (indicated by lower social approaches towards either freely moving or caged counterparts) and communication impairments (as assessed by a lower number of ultrasonic vocalization in response to maternal separation) (Bortolato et al., 2013a). In addition, MAO A KO mice display perseverative responses across several behavioral tasks, including marble burying, hole-board exploration and spontaneous alternations in a T maze (Bortolato et al., 2013a). Along the same lines, these mutants do not show any alterations in learning, but do exhibit reduced learning reversal in the Morris Water maze (Bortolato et al., 2013a), in alignment with a greater tendency to retain aversive memories (Kim et al., 1997; Dubrovina et al., 2006). MAO A KO mice also exhibit sensory and motoric alterations akin to those observed in ASD, including impairments in gait, hearing and sensorimotor integration (Cases et al., 1995; Thompson and Thompson, 2009; Bortolato et al., 2013). The examination of morphological and cytoarchitectonic changes in MAO A KO mice revealed a number of deficits in cortical architecture, including reduced callosal thickness in the rostral region (Bortolato et al., 2013a) and dysmorphism of barrel fields in layer IV of the somatosensory cortex (Cases et al., 1995). These formations, which regulate the sensory input from mistacial vibrissae, are typically studied as models of cortical columnar organization (Erzurumlu and Gaspar, 2012), a morphological characteristic typically impaired in ASD (Minshew and Williams, 2007; Hustler and Casanova, 2016). The abnormalities of the barrel field have been shown to reflect the hyperactivation of 5-$HT_{1B/1D}$ receptors in thalamocortical projections during the first two weeks of postnatal life (Salichon et al., 2001; Vitalis et al., 1998).

The neurobehavioral deficits in MAO A KO mice are typically preceded by alterations in their spontaneous behavior in early development. Whereas MAO A KO pups display several

abnormalities of their motoric behavior, including head bobbing and deficits in their righting reflex, adolescent MAO A KO mice exhibit hyperlocomotion and hyperreactivity to most stimuli (Cases et al., 1995).

The finding of autistic-like phenotypes in MAO A KO mice was strikingly confirmed by later clinical findings. Indeed, in 2014, the employment of targeted high-throughput sequencing methodologies in a broad sample of individuals with intellectual disability enabled the identification of a new case of *MAOA* deficiency in a 7-year old boy diagnosed with ASD, attention deficit and self-injurious behavior (Piton et al., 2014). The corresponding mutation was a substitution of cysteine 266 to a phenylalanine, which caused a drastic reduction in catalytic activity, estimated to be 10–40 times lower than normal levels (Piton et al., 2014). Two maternal uncles were also reported to harbor the same mutation, but, likely due to a history of maltreatment and sexual abuse in childhood, had a much more marked expressivity, with severe delays in psychomotor development, inability to read or write and poor autonomy. Similar to the patients described in the first report by Brunner and colleagues, these individuals exhibited sleep disturbances and repetitive behaviors. While severe aggressiveness was still present in these individuals, it was often reported to be addressed to the self (even though the two uncles had also a history of hetero-aggressive episodes).

A third description of Brunner syndrome was recently provided by Palmer and colleagues (2016). These authors documented two Australian families with different mutations of *MAOA* gene (a single-base pair insertion in exon 5 leading to a truncated protein, and an arginine-to-tryptophan substitution on codon 45, respectively). Affected males in both pedigrees had mild intellectual disability, introverted behavior, and occasional temper tantrums and other episodes of explosive aggression. Additional behavioral alterations ranged from obsessive behaviors and hoarding to attentional deficits and perseverations. Biochemical abnormalities in urinary profiles were the same as those described in other Brunner syndrome patients.

These cases collectively point to Brunner syndrome as a condition characterized by mild intellectual disability, often accompanied by other autistic-like traits, such as socio-communicative deficits and perseverative behaviors; thus, while impulsive aggressive outbursts were originally regarded as the core characteristic of this syndrome, these recent descriptions have emphasized that this behavioral trait is better contextualized as a maladaptive reaction to stress, and its severity may be influenced by the exposure to early adversity. From this perspective, it is also worth noting that aggression is a relatively common feature in ASD patients (Fitzpatrick et al., 2016), particularly with intellectual disability (Matson and Rivet, 2008), and typically signals an explosive reaction to frustrating environmental stimuli.

The neurodevelopmental nature of Brunner syndrome highlights the key role of early monoaminergic imbalances in its ontogenesis. Accordingly, we have recently shown that perseverative behavior in MAO A KO mice is ablated by inhibition of serotonin synthesis (Bortolato et al., 2013b). However, the same pharmacological manipulation did not reduce aggression (Bortolato et al., 2013b), pointing to the possibility that this response may be

contributed by other factors. In line with this interpretation, Yu and colleagues showed that enhancement of dopamine signaling during early adolescence may be primarily responsible for the aggressive responses consequent to *Maoa* deficiency in mice (Yu et al., 2014). The idea that early MAO A inactivation is critical for the ontogeny of antisocial behavior is also confirmed by other authors, who documented that treatment with MAO inhibitors in early developmental stages, but not in adulthood, results in behavioral alterations and morphological changes in thalamocortical development akin to those observed in MAO A KO mice (Whitaker-Azmitia et al., 1994; Boylan et al., 2000; Meija et al., 2002). It should also be noted, however, that the behavioral changes in MAO A KO mice were significantly reduced after acute treatment in adulthood with the serotonin reuptake inhibitor fluoxetine (Godar et al., 2014). In striking analogy with our findings, treatment with other serotonin reuptake inhibitors (sertraline and venlafaxine) led to behavioral improvements in some cases of Brunner syndrome, particularly in association with appropriate dietary modifications (Palmer et al., 2016). Overall, the fact that discoveries in MAO A KO mice preceded and informed both diagnostic and therapeutic information on Brunner syndrome strongly underscores the high translational value of these animal models.

Irrespective of the characteristics of Brunner syndrome, the role of MAOA in behavioral regulation has been particularly studied in relation to its polymorphic variants, and particularly its upstream variable-number repeat polymorphism (uVNTR), located 1.2 kb upstream of MAOA transcription initiation site (Sabol et al., 1998). This polymorphism has been studied extensively, in consideration of its functional nature, which has been revealed by the association of specific haplotypes with different MAOA activity levels. Six variants have been described, featuring different numbers of repeat sequences (Huang et al., 2004). The 3-repeat (3R) and 4-repeat variants are the most abundantly distributed (Sabol et al., 1998; Deckert et al., 1999; Jonsson et al., 2000). Of these, the 4R variant has been associated with higher transcriptional efficiency, and enzymatic activity Sabol et al., 1998; Deckert et al., 1999; Denney et al., 1999). The 3-repeat variant, associated with lower MAOA catalytic activity, has been found to confer vulnerability for several problems, including impulsive aggression and antisocial behavior (Samochowiec et al., 1999; Contini et al., 2006; Oreland et al., 2007; Buckholtz and Meyer-Lindenberg, 2008; Williams et al., 2009), alterations in the processing of facial affect (Lee and Ham, 2008). Neuroimaging studies have revealed that male carriers of low-activity uVNTR alleles exhibit morphological alterations of the orbitofrontal cortex (Meyer-Lindenberg et al., 2006; Cerasa et al., 2008; 2010) and functional abnormalities of the amygdala and hippocampus (Meyer-Lindenberg et al., 2006; Passamonti et al., 2006). Importantly, these changes appear to predispose to hostile attribution bias in these individuals (for a full discussion of the problem, the interested reader is referred to Godar et al., 2016). This neurobiological substrate appears to be particularly important in influencing the ontogeny of reactive aggression particularly in individuals with a history of early abuse and/or neglect (Caspi et al., 2002; Foley et al., 2004: Huang et al., 2004; Kim-Cohen et al., 2006; Rich-Edwards et al., 2010). The interaction between low MAO A activity and early trauma is particularly interesting, and likely follows the same mechanisms by which early adversity can exacerbate the cognitive and behavioral outcomes of *MAOA* deficiency, as evidenced by some of the clinical cases of Brunner syndrome documented by Pitot and colleagues (2014). Further studies will be

needed to document the neurobiological processes supporting how the interaction of MAOA and early maltreatment can increase the risk of antisocial behavior.

Neurobehavioral outcomes of *MAOB* deficiency

In striking contrast with the evidence on *MAOA* deficiency, the clinical consequences of low MAO B activity remain partially elusive. Indeed, the only cases with a documented loss-of-function mutation were described in atypical Norrie disease patients, harboring deletions of both the *ND* gene as well as the (adjacent) *MAOB* gene (Lenders et al., 1996). These patients did not exhibit any overt psychopathological alterations, pointing to a lack of overt clinical sequelae of *MAOB* deficiency (Lenders et al., 1996). In apparent contrast with this evidence, low MAO B activity in platelets – a highly heritable trait (Oxiensterna et al., 1986; Pedersen et al., 1993) that has been shown to be related to genetic variants with an A allele in intron 13 of the *MAOB* gene (Garpenstrand et al., 2000) – has been consistently associated with psychological characteristics related to impulsivity, including novelty- and sensation-seeking, extraversion, behavioral disinhibition and risk taking (Buchsbaum et al., 1976; Fowler et al., 1980; Reist et al., 1990; von Knorring et al., 1984; Blanco et al., 1996; Oreland and Hallman, 1995). The nature of these associations was originally questioned following the discovery that MAO B activity is reduced by tobacco use (Fowler et al., 1998), a habit highly associated with sensation-seeking (Doran et al., 2011). However, subsequent studies confirmed the association between low MAO B activity and novelty-seeking even after controlling for tobacco smoke (Ruchkin et al., 2005).

Complementary evidence on the phenotype of MAO B deficit has come from the behavioral characterization of MAO B KO mice (Grimsby et al., 1997), which were generated by insertion of a neomycin resistance cassette in exon 6 of *Maob* gene. In contrast with MAO A KO mice, MAO B KO mice do not exhibit overt deficits across most behavioral paradigms. However, MAO B KO mice did display a reduced level of depression-like responses in the forced swim test (Grimsby et al., 1997), as well as subtle reductions in anxiety-like behaviors that were best revealed in conditions of low environmental light (Bortolato et al., 2009). Indeed, a refined characterization of the behavioral features of MAO B KO mice showed that these mutants exhibit higher novelty-seeking responses and lower neophobia, in association with a marked proclivity to engage in risky tasks, such as crossing a wire-beam suspended bridge (Bortolato et al., 2009). Overall, these results confirm that MAO B deficiency results in behavioral characteristics that, while not intrinsically pathological, may be associated with higher venturesomeness and impulsivity. It is thus possible that MAO B deficiency may predispose to impulse-control problems or other psychopathological conditions characterized by impulsivity, such as substance abuse or ADHD. Indeed, several genetic studies have highlighted an association between numerous *MAOB* variants and ADHD (Li et al., 2008; Ribases et al., 2009; Karmakar et al., 2016; 2017). The association between low MAO B activity and ADHD has also been identified in several other studies (Shekim et al., 1986; Coccini et al., 2009; Nedic et al., 2010).

The behavioral sequelae of MAO B deficiency are unlikely to be reflective of early neurodevelopmental problems (given the lower expression of this enzyme in perinatal stages), but may instead reflect tonic enhancements of PEA and/or other MAO B substrates.

PEA is a trace amine that has been involved in several neuropsychiatric disorders (Beckmann et al., 1983; Szymanski et al., 1987; O'Reilly et al., 1991; Berry, 2007). The effects of PEA are not fully clear, but its chemical similarity with *d*-amphetamine (in which a methyl group is substituted at the α-carbon) underlines the possibility that this molecule may serve as a facilitator of catecholamine and serotonin release. On the other hand, the identification of TAAR1 as the endogenous receptor for PEA, as well as other monoamines metabolized by MAO B (such as tyramine and 3-iodothyronamine), calls into question whether the effects of PEA may result from a combination of different mechanisms. To date, the role of TAAR1 remains unclear, but it is likely that its activation may reduce, rather than increase, dopamine release, given that its agonists lower hyperlocomotion in hyperdopaminergic conditions (Revel et al., 2011; 2013); this role may be contributed by several converging mechanisms, including the involvement of potassium currents, heterodimerization with D2 dopamine receptors, β-arrestin recruitment and cross-talk with dopamine transporters (Rutigliano et al., 2018). In addition to TAAR1, TAAR4 has been shown to be activated by PEA (Borowsky et al., 2001; Liberles and Buck, 2006), even though these effects may be less important in humans, given that this molecule is a pseudogene in most primates, including humans (Stäubert et al., 2018) and that the concentrations of PEA required to activate this receptor may be beyond the physiological level range (Lindemann et al., 2005). Of note, all other TAAR receptors are refractory to the effects of PEA (for a review of the topic, see Zucchi et al., 2006). Finally, PEA has been shown to have a high affinity for σ2 receptor (Fontanilla et al., 2009), which has long been identified as a key regulator of dopaminergic transmission (Guo and Zhen, 2015), and, particularly, of D1 dopamine receptor signaling (Aguinaga et al., 2018). Notably, this receptor has been recently identified as TMEM97, an endoplasmic reticulum-transmembrane protein that regulates the sterol transporter NPC1 (Alon et al., 2017). The functional link between PEA and cholesterol homeostasis, however, remains poorly understood.

PEA is involved in the modulation of emotional responses, including arousal, exploration and reinforcement (Sabelli and Javaid, 1995). MAO B KO mice exhibit high levels of PEA in the striatum, possibly pointing to alterations in dopamine release in this region. Indeed, PEA plays an important role in the regulation of dopamine functions (Kuroki et al., 1990; Sotnikova et al., 2004). Given the relevance of dopamine in behavioral disinhibition (Black et al., 2002; Megens et al., 1992; van Gaalen et al., 2006) and anxiety (Shabanov et al., 2005; Picazo et al., 2009), this neurotransmitter may be directly implicated in the ontogeny of the behavioral characteristics of MAO B KO mice. Notably, MAO B KO mice are also oversensitive to D1 dopamine receptor activation (Chen et al., 1999). Future studies will be needed to understand whether the antagonism of TAAR1 receptors and/or modulation of dopaminergic neurotransmission may rectify the behavioral abnormalities in MAO B KO mice.

Neurobehavioral outcomes of combined *MAOA* and *MAOB* deficiency

The phenotypical characteristics of combined MAO deficiency were originally reported in a few cases of atypical Norrie disease. In these patients, large deletions in the X chromosome encompassed the *ND*, *MAOA* and *MAOB* genes. The resulting syndrome included severe developmental deficits (in addition to the sensory problems secondary to Norrie disease),

including autistic-like behaviors and severe cognitive delay (Sims et al., 1989; Murphy et al., 1990' Collins et al., 1992). In 2010, Whibley and coworkers reported the first case of total MAO deficiency (without Norrie disease) in two siblings with major developmental delay, mental retardation and stereotypical movements (hand-flapping and lip-smacking). The characteristics of this syndrome were reported to be similar to Rett syndrome and ASD (Whibley et al., 2010). Both affected brothers exhibited several episodes of hypotonia in perinatal stages, which was not reversed by anticonvulsants. One patient, who died at 5 years of age, was found to display loss of Purkinje cells in the cerebellum and cortical neurons (Whibley et al., 2010). Similar features were described in other two Japanese siblings with *MAOA* and *MAOB* deletion (Saito et al., 2014).

The double mutation of MAO in mice was originally observed in a colony of MAO B KO mice (Chen et al., 2004) by spontaneous mutation of *Maoa* gene. The validation of the line showed an increase in brain levels of 5-HT (850%), NE (220%), DA (170%) and PEA (1570%) of MAO A/B KO mice as compared to WT littermates. The magnitude of these increases is much greater than those seen in either KO line, suggesting a cooperativeness of the two enzymes in serving similar catalytic roles. Phenotypic analyses of MAO A/B KO mice have clearly identified an autistic-like phenotype and cognitive deficits generally more severe than that manifested by congenic MAO A KO mice (Bortolato et al., 2013; Singh et al., 2014). In line with clinical evidence, MAO A/B KO mice display a significant reduction in weight, elevated levels of intermale aggression, overgeneralized fear conditioning, socio-communicative deficits, and perseverative behaviors (Chen et al., 2004; Bortolato et al., 2013; Singh et al., 2014). The neuropathological alterations featured by MAO A/B KO mice are also similar, yet more severe, than those shown by MAO A KO counterparts. In particular, these mutants exhibit alterations in cerebellar architecture (with a loss of Purkinje cells) and reduced thickness of the rostral corpus callosum (Bortolato et al., 2013). The cause of these abnormalities is likely primarily contributed by high levels of serotonin, particularly in early development (Cheng et al., 2010). The role of early-life serotonin in MAO A/B KO mice is indirectly confirmed by other findings on the abnormal neurogenesis in these mice (Cheng et al., 2010). Indeed, such deficits were rescued by the administration of inhibitors of serotonin synthesis in late embryonic stages (Cheng et al., 2010). In line with this idea, early serotonergic abnormalities are a well-known risk factor for ASD pathogenesis (Muller et al., 2016), even though the specific receptors whereby this neurotransmitter can influence corticogenesis and synaptic connectivity in the cortex remain poorly understood.

Conclusions

Since the identification of *MAOA* and *MAOB* genes in 1988 (Bach et al., 1988), complementary strategies have been instrumental to understand the functional characteristics of these enzymes, as well as the pathogenesis of disorders linked to these genes. Our discoveries in animal models have shown that MAO A deficiency results in a spectrum of intellectual disability and socio-communicative deficits, which encompass both antisocial behavior and ASD-like features. These characteristics are exacerbated by a concomitant MAO B deficiency, with a more prominent set of ASD-related features. These findings point to a cooperative action of the two enzymes in serving similar catalytic functions, particularly

with respect to serotonin, the elevation of which may lead to a facilitation of ASD pathogenesis. However, it is also possible that the behavioral inhibition associated with *MAOB* deficiency, by strengthening the actions of the mesolimbic system, may in turn compound corticolimbic imbalances in association with the cognitive deficits resulting from *MAOA* deficiency. While MAO deficiency syndromes remain rare (and, in the case of *MAOB*, may not reach a significant psychopathological impairment to be clinically relevant, at least by itself), the lesson provided by clinical and preclinical evidence has elucidated novel, unexpected links between ASD, impulse-control disorders and antisocial behavior. Although caution should be advocated when extrapolating data from mouse models to humans, these new prospects warrant future explorations, particularly with respect to the timing and monoaminergic mechanisms of their neurodevelopmental underpinnings.

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