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Monoamine Oxidase in Neuropsychiatry and Behavior

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Monoamine oxidase (MAO) catalyzes the oxidative deamination of a number of biogenic amines, including the key neurotransmitters serotonin (5-HT), norepinephrine (NE), and dopamine (DA) and the neuromodulator phenylethylamine (PEA). Two forms of MAO, designated "MAO A" and "MAO B," have been identified on the basis of biochemical properties and, subsequently, by cloning the relevant genes. Of the two, MAO A exhibits a higher affinity for 5-HT and NE and for the inhibitor clorgyline (Johnston 1968), whereas MAO B has a higher affinity for PEA, benzylamine, and the inhibitor deprenyl (Knoll and Magyar 1972). DA is a substrate for both MAO A and MAO B. Although most tissues express both isoenzymes, human placenta and fibroblasts express predominantly MAO A, and platelets and lymphocytes express only MAO B (for review, see Shih et al. 1999).

The ability of the MAOs to catabolize neurotransmitters has made these enzymes attractive candidates in the study of neurological diseases and psychiatric and behavioral traits. Indeed, even before the genes for MAO A and B were cloned, the role of MAO B in psychiatric disorders was widely studied. Platelets, which are easily obtained and lack MAO A expression, were the cell type of choice for much of this work. Low platelet MAO B activity has been associated with bipolar disorder, suicidal behavior, and alcoholism (Devor et al. 1993), as well as with sensation seeking and poor impulse control (Oreland 1993; Holschneider and Shih 1998). However, much of this biochemical work may need to be revisited, given the recent finding that smoking inhibits both MAO A activity and MAO B activity (Fowler et al. 1996*a*, 1996*b*). For instance, after correcting for the effect of smoking, Simpson et al. (1999) determined that MAO B activity is not significantly reduced in schizophrenics. With the successful cloning of human liver MAO A and B, Bach et al. (1988) demonstrated that MAO A and B are distinct, but closely related, X-linked genes (Shih 1991). The MAO A and MAO B genomic sequences (Grimsby et al. 1991; Chen et al. 1992) and promoters (Zhu et al. 1992; Zhu and Shih 1997) have been studied extensively in the pursuit of polymorphisms that might show these genes to be associated with psychiatric disorders and behaviors. Perhaps the most intriguing finding to emerge to date implicates MAO A in the control of aggressive behavior in humans, a finding that we and our collaborators have pursued in a knockout-mouse model.

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Deletion of *MAOA* and *MAOB* in Norrie disease

The gene for Norrie disease (*ND*) and the genes *MAOA* and *MAOB* are arranged in tandem on human Xp11.2-11.4 (Chen et al. 1995). Deletion of *ND* is sometimes accompanied by deletion of one or both of the MAO genes and causes congenital blindness due to the disrupted development and degeneration of the neuroretina (Berger et al. 1992). More than one-third of ND patients also develop progressive hearing loss and manifest mental retardation or psychoses (Sims et al. 1989). Two such patients, studied in detail by Sims et al. (1989) and Lenders et al. (1996), lack detectable MAO B activity in their platelets and do not express MAO A mRNA in their fibroblasts, and they show elevated plasma and urine levels of NE, DA, 5-HT, and PEA. Two brothers with a contiguous-gene deletion encompassing ND and MAO B show an increase in urinary PEA levels, but their levels of 5-HT, NE, and DA are normal (Lenders et al. 1996). These neurochemical changes are consistent with the findings in *Maoa*-knockout (Cases et al. 1995) and *Maob*-knockout (Grimsby et al. 1997) mice.

The clearest genetic evidence that the MAOs regulate human behavior comes from the work of Brunner et al. (1993*a*, 1993*b*), who studied a Dutch family in which eight males manifest a complex behavioral syndrome that includes borderline mental retardation and impulsive aggression. Sequencing of the *MAOA* gene showed,

at position 936, a C→T mutation that introduces a premature-termination codon and that creates a null allele in the gene. Urine samples from these affected males showed decreased levels of 5-hydroxyindolecetic acid, homovanillic acid, and 3-methoxy-4-hydroxyphenylethyleneglycol (Brunner et al. 1993*a*, 1993*b*), which are the degradation products of 5-HT, DA, and NE, respectively. Further studies are required to establish the frequency of this mutation in humans, but urine analysis of 119 inmates from a prison in Taiwan showed no evidence for altered monoamine metabolism, suggesting MAO A deficiency (H. M. Hwang and J. C. Shih, unpublished data). The aggressive behavior seen in men lacking MAO A may, however, be unrelated to this genetic defect; environmental substances, stress, drugs, or, perhaps, other genetic factors in this family may increase the susceptibility of these men to aggression. However, as discussed below, the relationship between MAO A deficiency and aggression has also been confirmed in studies of MAO A–deficient mice.

Behavioral Phenotypes and MAO-Gene Polymorphisms

The *MAOA* and *MAOB* sequences have been scrutinized for the existence of polymorphisms that might be associated with other psychiatric phenotypes. Table 1 describes the *MAOA* polymorphisms that have been reported to be associated with such behavioral phenotypes as aggression and substance abuse (see Reich et al. 1999 [in this issue]), as well as affective disorders, such as bipolar and panic disorder. As is common in such studies (see O'Donovan and Owens 1999 [in this issue]), associations with these phenotypes prove difficult to replicate, and both confirmatory and negative findings are presented in the table. Polymorphisms in the *MAOB* gene have also been identified, but no behavioral or psychiatric phenotypes have yet been associated with these variants. Most of the known *MAOA* polymorphisms either affect intronic sequences or introduce a silent change in the open-reading-frame polymorphisms (i.e., the *Eco*RV and *Fnu*4HI polymorphisms); these variants are unlikely to affect MAO function, although they may be in disequilibrium with other, as yet unidentified, functional variants. Recently, however, a VNTR polymorphism that affects transcriptional activity has been found in the *MAOA*-gene promoter (Zhu et al. 1992, 1994; Sabol et al. 1998). This variant, which is associated with lower levels of MAO A activity, occurs with a higher-than-normal frequency in patients with panic disorder (Deckert et al. 1999) but never occurs in patients with antisocial personality disorder (Lu et al. 1999).

Behavioral and Metabolic Features of MAO A–Deficient Mice

To test the role of MAO A in behavior in a system that permits experimental manipulation, we established a line of mice with a targeted disruption of the *Maoa* gene (Cases et al. 1995). We observed that males in this strain exhibit a significant increase in brain levels of 5-HT and NE and a modest increase in DA, confirming that the substrate specificities of the mouse MAOs are similar to those in humans. Crucially, these males manifest enhanced aggression, as assessed by observation of confrontations between intruder and resident mice under standardized conditions (Cases et al. 1995; Shih et al. 1999).

Table 1

Polymorphisms of the MAO A Gene which May Be Associated with Psychiatric Disorders and Behaviors

Polymorphism	Disorder/Behavior	Association	Reference(s)
23-bp VNTR in intron 1	Tourette syndrome and drug abuse	Yes	Gade et al. (1998)
	Bipolar disorder	No	Craddock et al. (1995); Lim et al. (1995); Muramatsu et al. (1997)
$(GT)_n$ repeat in intron 2	Bipolar disorder	Yes	Lim et al. (1995)
	Bipolar disorder	No	Craddock et al. (1995); Muramatsu et al. (1997); Parsian and Todd (1997)
	Alcoholism	Yes	Parsian et al. (1995); Vanyukov et al. (1995); Hsu et al. (1996)
	Aggression	No	Vanyukov et al. (1995)
C→T mutation in exon 8	Aggression	Yes	Brunner et al. (1993*a*)
*Fnu*4HI-RFLP in exon 8	Bipolar disorder	No	Craddock et al. (1995); Lim et al. (1995); Muramatsu et al. (1997)
	Alcoholism	No	Hsu et al. (1996)
*Eco*RV polymorphism in exon 14	Obsessive-compulsive disorder	Yes	Camarena et al. (1998)
	Antisocial personality disorder	No	Lu et al. (1999)
	Schizophrenia	No	Coron et al. (1996)
VNTR in the promoter	Panic disorder	Yes	Deckert et al. (1999)
	Antisocial personality disorder	No	Lu et al. (1999)

Drug studies lend further support to the notion that high CNS levels of monoamine neurotransmitters promote aggressive behavior. Ketanserin and tetrabenazine (TBZ) both act as antagonists of the vesicular monoamine transporter VMAT2 (Leysen et al. 1988; Roth et al. 1987), and ketanserin also interferes with 5-HT, by blocking 5-HT_{2A} receptors. As shown in figure 1, both of these drugs diminish the aggressive behavior of MAO A–deficient mice in a dose-dependent manner (Shih et al., in press). These drugs also inhibit the behavior of wild-type mice, but the aggression is much lower in the wild-type animals when compared with the *Maoa*-knockout mice. Thus, untreated wild-type males exhibit aggressive behavior for 48.7 ± 18.0 s during the first 10 min after a resident and an intruder animal begin to fight; with mice of the *Maoa*-knockout genotype, the aggression occurs for 93.2 ± 28.9 s. The antiaggressive effect of TBZ and at least part of the effect of ketanserin may be mediated by their effects on VMAT2.

MAO A–deficient mice also show more efficient emotional learning than do wild-type animals, by several measures, including the freezing-response-after-foot-shock training (Kim et al. 1997). Evidently, fear-conditioned learning is enhanced in these mice as a result of their elevated monoamine levels. This learning phenotype is consistent both with earlier pharmacological studies, which showed that the injection of monoamines into the brains of mice increases fear-memory learning, and with subsequent work with drugs that lower the levels of monoamines, which are found to interfere with this type of learning.

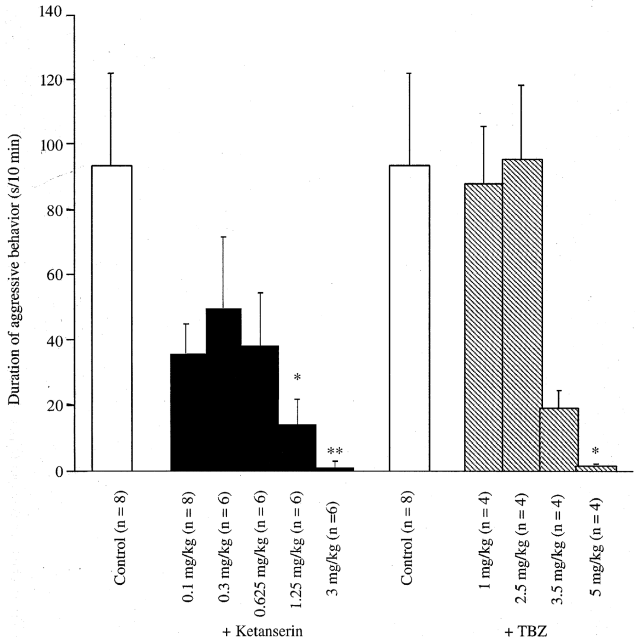

Figure 1 Effect of ketanserin and TBZ on aggressive behavior of MAO A–deficient mice in resident-intruder confrontations. The duration of aggressive behavior of the more aggressive mouse in each pair is expressed in seconds (s) during the first 10 min after the first attack. *n* = the number of mouse pairs in each condition. Multiway comparisons are by one-way ANOVA and the Tukey-Kramer test for control versus drug-treated mice. A single asterisk (*) denotes $P < .05$, and double asterisks (**) denote $P < .01$. Data are from Shih et al. (in press).

Structural and Developmental Changes in MAO A–Deficient Brains in Mice

In addition to these behavioral differences between *Maoa*-knockout and wild-type mice, the phenotype of the knockout animals includes some subtle changes in neuronal structure and patterns of gene expression in the brain. The absence of MAO A activity affects the distribution throughout development of 5-HT and of factors that interact with it. Immunolabeling experiments show that 5-HT accumulates transiently at numerous atypical locations during the embryonic and postnatal development of *Maoa*-knockout mice, including sites within the telencephalon, the diencephalon, and the brain stem (Cases et al. 1998). Interestingly, catecholaminergic cells at diverse sites, which would not be expected to express 5-HT, also display transient 5-HT immunoreactivity, perhaps as a result of 5-HT uptake via the DA or NE plasma-membrane transporter. It appears that neuron populations that form highly precise projection maps could be affected by excess 5-HT during development (Cases et al. 1998), and, indeed, the increased 5-HT levels in brains from *Maoa*-knockout pups causes cytoarchitectural alterations in the somatosensory cortex. As Cases et al. (1996, 1998) have shown, these changes in brain structure may be related to the enhanced aggression of MAO A–deficient mice, because administration of *p*-chlorophenylalanine—which inhibits tryptophan hydroxylase, the rate-limiting enzyme in 5-HT biosynthesis—reverses both the structural changes and the aggressive behavior of adults (Cases et al. 1996). Further clues to the brain structures involved in aggression come from the work of Shi et al. (1998), who used a tissue-specific promoter to restore MAOA expression specifically to the forebrain of *Maoa*-knockout animals. The duration of aggressive behavior is reduced to normal levels in these transgenic mice, suggesting that the lack of MAO A in the forebrain of *Maoa*-knockout mice underlies their enhanced aggression.

Radio-ligand binding and autoradiography have also shown that the numbers of sites that are positive for VMAT2, 5-HT_{1A}, 5-HT_{2A}, or 5-HT_{2C} are decreased in brains of MAO A–deficient mice (Shih et al. in press), perhaps because the excess ligand causes these factors to be down-regulated. Interestingly, however, MAO B does not appear to be altered in its expression level in

Maoa-knockout mice. The apparent absence of compensatory changes in expression may make these mutant animals valuable tools to study the distribution and function of MAO B. Brains of *Maoa*-knockout pups accumulate 5-HT at a concentration nine times higher than do wild-type mice at the same stage (Cases et al. 1995), but in adult animals the difference is only twofold. This change probably indicates that MAO B is capable of oxidation of 5-HT in vivo in the absence of MAO A, and its timing may reflect the late expression of MAO B. Thus, it is reasonable to speculate that 5-HT would be greatly enhanced in mice deficient for both MAO genes. We are currently generating *Maoa/Maob*–double-knockout mice, which may recapitulate some of the features of the patients with ND that have been discussed above. The development of mice lacking both MAO A and MAO B should allow us to explore the genetic interactions between *Maoa* and *Maob* in both neural development and the control of behavior.

Grimsby et al. (1997) showed that the brain level of PEA is eightfold higher in *Maob*-knockout mice than in wild types, although 5-HT, NE, and DA levels are not altered. The effect of MAO B on PEA is consistent with findings in patients with ND who lack MAO B expression (Lenders et al. 1996) and with suggestions that this neurotransmitter may modulate mood and affect (Linnoila et al. 1983).

Concluding Remarks

The role of MAO A in aggression, first identified by Brunner et al. (1993*a*, 1993*b*), has been confirmed in MAO A–deficient mice, which, like the men in the Dutch family, show increased brain levels of 5-HT, NE, and DA and manifest enhanced aggression. However, aggression is a complicated behavior, and mice that lack any of several genes also manifest altered aggression, including those for the adenosine 2a receptor (Ledent et al. 1997), estrogen receptor (Ogawa et al. 1996), 5-HT_{1B} receptor (Ramboz et al. 1996), bcr (a GTPase-activating protein for Rac [Voncken et al. 1998]), CaMKIIα (Mayford et al. 1996), catechol-o-methyltransferase (Gogos et al. 1998), nitric oxide synthase (Kriegsfeld et al. 1997), and oxytocin (DeVries et al. 1997). To date, no lesions in these genes in humans have been reported, and these mouse data have yet to be applied to the treatment of behavioral or psychiatric disorders. Most of the drugs now used to treat aggressive behavior act on brain DA, 5-HT, and α-aminobutyric acid-receptor subtypes (Miczek et al. 1994). However, these medications, including benzodiazepines and antipsychotics, treat aggression largely by sedating the patient. Doses of ketanserin and TBZ, which abolish the aggressive behavior of MAO A–deficient mice, on the other hand, do not produce sedation (Shih et al., in press). Therefore, ketanserin and TBZ may be developed as novel antiaggressive agents. Further studies using *Maoa*- and *Maob*-knockout mice will provide new insights into human neuropsychiatric disorders. New techniques, such as cDNA expression arrays, may help to detect new genes and polymorphisms that are associated with neuropsychiatric disorders and behaviors.

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