Monoamine Oxidase A Gene Promoter Variation and Rearing Experience Influences Aggressive Behavior in Rhesus Monkeys

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Background: *Allelic variation of the monoamine oxidase A (MAOA) gene has been implicated in conduct disorder and antisocial, aggressive behavior in humans when associated with early adverse experiences. We tested the hypothesis that a repeat polymorphism in the rhesus macaque MAOA gene promoter region influences aggressive behavior in male subjects.*

Methods: *Forty-five unrelated male monkeys raised with or without their mothers were tested for competitive and social group aggression. Functional activity of the MAOA gene promoter polymorphism was determined and genotypes scored for assessing genetic and environmental influences on aggression.*

Results: *Transcription of the MAOA gene in rhesus monkeys is modulated by an orthologous polymorphism (rhMAOA-LPR) in its upstream regulatory region. High- and low-activity alleles of the rhMAOA-LPR show a genotype × environment interaction effect on aggressive behavior, such that mother-reared male monkeys with the low-activity-associated allele had higher aggression scores.*

Conclusions: *These results suggest that the behavioral expression of allelic variation in MAOA activity is sensitive to social experiences early in development and that its functional outcome might depend on social context.*

Key Words: MAOA, promoter, VNTR, rearing, aggression, rhesus

The interaction between genes and environment has long been acknowledged to account for significant individual variation in susceptibility or resilience to risk factors. One aspect of "environment" that is thought to play a critical role in modifying the influence of genes that convey risk for complex behavioral disorders is one's early experience, particularly during infancy and early childhood; however, identification of genetic risk factors that can be modified by protective environmental conditions or exacerbated by adverse experiences remains largely undetermined for complex psychiatric and behavioral disorders, as does isolation of genetic variants that increase resilience or vulnerability to environmental risks.

Monoamine oxidase A (MAOA [EC 1.4.3.4]), located on chromosome Xp11.3, oxidizes the amine neurotransmitters serotonin, dopamine, and norepinephrine and is expressed in a cell type–specific manner (Shih 1991; Thorpe et al 1987). In humans, low MAOA activity is associated with impulsive behavior and conduct disorder (Gabel et al 1995; Lawson et al 2003), and gene variants that result in low MAOA activity are implicated in the pathogenesis of aggression and impulsive violence (Brunner et al 1993; Shih et al 1999; but see Manuck et al 2000, 2002). A hemizygous chain termination mutation in exon 8 of the MAOA gene is linked to mild mental retardation and occasional episodes of impulsive aggression, arson, and hypersexual behavior, such as attempted rape and exhibitionism, in affected male subjects from a single large family (Brunner et al 1993). Affected male subjects exhibit markedly disturbed monoamine metabolism and an absence of MAOA enzymatic activity in cultured fibroblasts. Although inhibition of MAOA in adults leads to antidepressant effects but not aggression-related behavior, the deviate behavior in MAOA-deficient men might be due to structural or compensatory changes resulting from altered monoamine metabolism during neurodevelopment. The behavioral consequences of targeted inactivation of MAOA in mice confirm the aggressive phenotype of the nonsense mutation in the human MAOA gene (Cases et al 1995; Seif and De Maeyer 1999). Mice deficient in MAOA display elevated brain levels of serotonin and increased reactivity to stress, hyperactive startle responses, violent motions during sleep and abnormal posture, and aggressive behavior. Resident–intruder tests elicited enhanced male aggressiveness and increased injury between male cage-mates.

A functional length polymorphism in the transcriptional control region for the MAOA gene (MAOA-LPR) affects transcriptional activity (Deckert et al 1999; Sabol et al 1998). Alleles associated with reduced in vitro MAOA activity were associated with antisocial behavior in one study of alcohol-dependent male subjects (Samochowiec et al 1999) but not in another (Koller et al 2003). Inferred high MAOA activity was associated with impulsivity, hostility, and lifetime aggression history in a community sample of men (Manuck et al 2000, 2002). Caspi et al (2002) reported a significant interaction between childhood maltreatment and low MAOA activity–associated alleles in modulating the risk for antisocial behavior, aggressiveness, and violence. These results were recently replicated by Foley et al (2004).

The role that early adverse experience plays in altering a constellation of physiologic and behavioral processes in nonhuman primates has been extensively studied. Harlow was the first to develop a nonhuman primate model of early adversity by rearing young monkeys in the relative social impoverishment of same-aged peers rather then with their mothers in normal social groups (Harlow and Harlow 1965). Research since then has clearly established that appropriate parental input is critically important for normative development of the hypothalamic–pituitary–adrenal axis and neurotransmitter system function (Higley et al 1994). Primates removed from their mothers and

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deprived of early participation in complex social groups later exhibit aberrations in neurochemical function, neuroendocrine stress axis activity, and in many aspects of social behavior; however, individual variation in susceptibility to environmental manipulation remains (Kraemer 1985; Suomi 1987). To date, few studies have isolated genetic sources for variation in response to early adverse rearing conditions in human or nonhuman primates. We recently demonstrated a gene × environment interaction between the rhesus macaque serotonin transporter gene promoter polymorphism and early rearing experience that accounts for some variation in the physiologic and behavioral outcome of early adverse environments (Barr et al 2003a; Bennett et al 2002; Champoux et al 2002). Indeed, nonhuman primates make excellent models for studying the relative contributions of genes and a stressful environment because, unlike humans, their environments can be controlled (Barr et al 2003b).

Here, we characterize the structure and functional impact of a repeat polymorphism in the transcriptional control region upstream of the rhesus monkey (Macaca mulatta) MAOA (rhMAOA-LPR) coding sequence that is orthologous to the MAOA-linked polymorphic region (MAOA-LPR) in humans. We tested the hypothesis that rhMAOA-LPR genotypes are associated with variation in aggressive behavior and that psychosocial stress following early parental absence influences the impact of allelic variation in MAOA function on social competence. We based our hypothesis on the observation that 1) pharmacologic or genetic manipulation of MAOA activity alters aggression-related behaviors in experimental animals; 2) genetic variation associated with low or absent MAOA activity is implicated in the pathogenesis of aggression and impulsive violence in humans and mice; and 3) childhood maltreatment modulates the MAOA-related risk for antisocial behavior, aggression, and violence.

Methods and Materials

Molecular Genetics

The rhMAOA-LPR is located 1.1 kilobases (kb) upstream of the MAOA transcription initiation site and is composed of 18-base-pair (bp) repeat elements (Figure 1). The sequence of the transcriptional control region of the rhMAOA gene (−1327 to −1 with respect to the translation initiation codon) was derived from a 1.3-kb clone rhMAP-1327 (EMBL-GenBank accession number AJ544234) that was isolated from genomic deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR)-with primers map1 5′-ATATACGCGTCCCAGGCTGCTCCAGAAAC-3′ and map2 5′-ATCTCGAGCTTTGGCTGACACGCTCCTG-3′. Blood for DNA isolation and analysis was obtained from male rhesus monkeys. Oligonucleotide primers flanking the rhMAOA-LPR and corresponding to the nucleotide positions −1327 to −1309 (malpr1, 5′-CCCAGGCTGCTCCAGAAAC) and −1103 to −1086 (malpr2, 5′-GGACCTGGGAAGTTGTGC) with respect to the translation initiation codon of the rhesus monkey MAOA gene 5′ flanking regulatory region were used to generate 206-, 224-, or 242-bp fragments. Polymerase chain reaction amplification (40 sec at 94°C, 40 sec at 55°C, 60 sec at 72°C for 35 cycles) was carried out in a final volume of 25 μL consisting of 60 ng genomic DNA, 200 μmol/L of each deoxynucleoside triphosphate, 2 mCi of [α ^{32}P]deoxycytidine triphosphate (10 mCi/mL, 300 Ci/mmol), 10 pmol of sense and antisense primers, 75 mmol/L Tris-HCl (pH 9.0), 20 mmol/L $(NH_4)_2SO_4$, 1.5 mmol/L $MgCl_2$, .01% Tween-20, and .2 units of Taq DNA polymerase. Polymerase chain reaction products were separated by electrophoresis through a 6% denaturing polyacrylamide gel and detected by autoradiography.

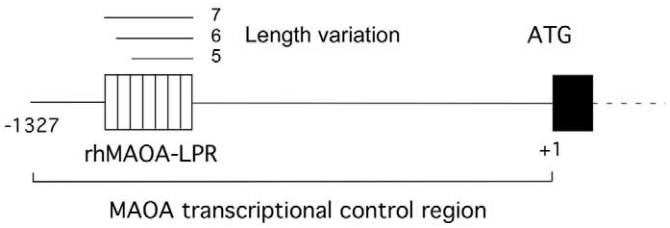

Figure 1. Map of the transcriptional control region of the rhesus monkey monoamine oxidase A (rhMAOA) gene-linked (EMBL-GenBank accession number AJ544234) polymorphic region. The rhMAOA-linked polymorphic region comprises an 18-bp repetitive sequence with length variation of 5–7 repeats.

For the generation of luciferase gene constructs, DNA fragments of rhMAP-1327 containing the 5-, 6-, and 7-repeat variants of the rhMAOA-LPR were ligated into the promoterless luciferase (luc+) expression vector pGL3 basic (Promega, Madison, Wisconsin). Inserts and insert-vector boundaries were verified by sequence analysis. Length variants of MAP-1327/luc+ constructs and controls were transiently expressed in SH-SY5Y human neuroblastoma cells, which constitutively express MAOA, and in MAOA-negative cos 7 (African green monkey kidney) cells (Klegeris and McGeer 2000). Cells were grown at 37°C in a humidified 5% CO_2 atmosphere in Dulbecco's modified Eagle's medium supplemented with 15% fetal calf serum, 50 μg/mL streptomycin, and 50 units/mL penicillin. Luc+ gene expression was studied relative to the pGL3 basic and pGL3 control vectors. Transfection efficiency was assessed by cotransfection with .5 μg of pCMV-lacZ vector. For transient expression, SH-SY5Y neuroblastoma cells (2×10^5) were exposed for 29 hours to 4 μg of luciferase constructs complexed with FuGENE 6 transfection reagent (Roche Diagnostics, Basel, Switzerland). After extraction in 250 μL of lysis buffer (Promega), luciferase activity was assayed by the addition of 10 μl of cell lysate at 15-sec intervals to 100 μL of luciferin reagent. The extract (10 μL) was also tested for b-galactosidase activity, and luciferase activities were normalized to b-galactosidase activities with equal amounts of total protein determined by the method of Bradford. Four independent experiments in triplicate with different plasmid preparations were performed.

Subjects

Behavioral data were collected from 45 male, group-housed rhesus macaques (Macaca mulatta) at the National Institutes of Health Animal Center. Subjects were selected from five birth cohorts born between 1991 and 1995 and were 3–5 years of age when tested. Individuals within cohort groups were less than 9 months apart in age. Only male monkeys were included in this study because their single X chromosome generates two rhMAOA-LPR genotypes with either high activity (5- and 6-repeat alleles) or low activity (7-repeat allele). Female animals were not included because they carry two copies of the X chromosome, homozygosity for the low-activity allele is rare, and it is not possible to determine which of the two alleles is inactivated in heterozygous female monkeys.The subjects were divided into two groups with different social and rearing experiences early in life, which fell into one of the following categories: 1) mother-reared, either reared with the biological mother or cross-fostered; or 2) peer-reared, with either continuous or daily, limited access to a peer group of three to four monkeys (Champoux et al 1999).

Peer-reared monkeys, selected randomly, were separated from their mothers shortly after birth, placed in the nursery, and given access to same-aged peers at 30 days of age either continuously or during daily play sessions. Mother-reared and cross-fostered monkeys remained with the mother (or foster mother), typically within a social group. At approximately 7 months of age, mother-reared monkeys were weaned and placed together with their peer-reared cohort in large, mixed-sex social groups. Protocols for the care and use of experimental animals were approved by the Institutional Animal Care and Use Committee of the National Institute on Alcohol Abuse and Alcoholism and the National Institute of Child Health and Human Development, National Institutes of Health.

Assessing Aggressive Behavior

Severe aggressive behavior within relatively small social groups of captive monkeys is generally infrequent. Therefore, we chose to assess individual aggression by using two types of aggressive behaviors that are commonly displayed in rhesus social groups: 1) dyadic food competition, whereby aggressive behavior was elicited by offering pairs of monkeys, matched for age and relative dominance rank, coveted, prized food items (e.g., grapes, peanuts, cereal, Prima-treats) in a competitive social situation with the frequency of wins/losses recorded; and 2) home cage social aggression, whereby aggressive acts were observed and recorded during normal social interactions in undisturbed daily observation sessions. The frequency of wins/losses during competitive aggression was converted to z scores to control for differences between testing sessions. The duration (in seconds) of threats, displacements, contact aggression, and other aggressive behaviors were recorded for each subject during three 30-min sessions. All behavioral observations were conducted before genotyping.

Statistics

We used analysis of variance (ANOVA) for testing associations between the independent variables of MAOA genotype and rearing condition and the dependent measures of aggression. Although our subjects derive from captive colony animals, we assembled a panel of subjects with an average idenity by descent of 1.68%, a measure of pairwise relatedness equivalent to eighth-degree relatives (third cousins), which is sufficiently low to be considered essentially unrelated (Robin et al 1997). On the basis of the functional assessment of rhMAOA-LPR variants, monkeys with high-activity 5- and 6-repeat alleles were combined for comparison with those with the low-activity 7-repeat allele. Animals were assigned nominal independent variables according to rhMAOA-LPR function (high activity vs. low activity) and rearing condition (peer-reared vs. mother-reared), to determine the effects of these variables on 1) aggression during food competition; and 2) home cage aggression. Analyses were performed with JMP statistical software (SAS Institute, Cary, North Carolina). Criterion for significance was set at $p < .05$.

Results

Polymerase chain reaction–based genotype analysis of 217 rhesus monkeys revealed three alleles of 5, 6, and 7 repeats (each 18 bp in length), with allele frequencies of 35% for the 5-repeat, 25% for the 6-repeat, and 40% for the 7-repeat allele. The activity of both the 5-and 6-repeat variant was approximately 26% higher than that of the 7-repeat form ($p < .005$) (Figure 2). When clustered by activity, the count and frequency of the high-activity group versus the low-activity group was 11 (.48) and 12 (.55), respectively, for the peer-reared and 7 (.32) and 15 (.68) for the mother-reared monkeys, with no significant differences in the genotype distribution for the two rearing groups [$\chi^2(1) = 1.2$, $p = .27$].

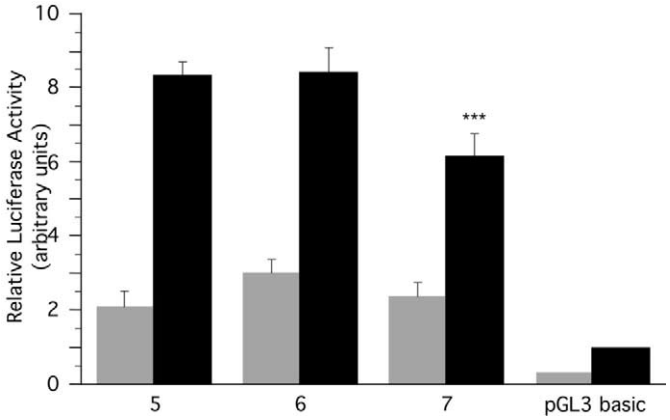

Figure 2. Transcriptional activity of the 5-, 6-, and 7-repeat rhMAOA-LPR variants in SH-SY5Y human neuroblastoma cells, which constitutively express MAOA (black bars) and in MAOA-negative cos 7 (gray bars). Results are means ± SD of four independent experiments in triplicate. The MAOA transcription control region (rhMAP-1327) containing the 5-, 6-, and 7-repeat variants of the rhMAOA-LPR was ligated into the promoterless luciferase (luc+) expression vector pGL3 basic. rhMAOA-LPR, rhesus monkey monoamine oxidase A gene-linked polymorphic region. ***$p < .005$ (one-way analysis of variance followed by Fisher's protected least significant difference test), 5- and 6-repeats (black bars) vs. 7-repeats (gray bars).

There was a significant genotype × rearing interaction on aggressive behavior during food competition ($F = 5.43$, $p = .03$) but no main effects of genotype or rearing (Figure 3). Post hoc tests (Fisher's protected least significant difference) indicated that mother-reared male monkeys with the low-activity genotype (mean z score = .88 ± .38) were significantly more aggressive than nursery-reared male monkeys with the low-activity genotype (mean z score = −31 ± .29) but not more so than male monkeys with the high-activity genotype, regardless of rearing experience (mean z score: mother-reared = −.19 ± .45; peer-reared = .34 ± .32). A similar pattern existed for aggressive behavior observed during normal home cage social interactions. There was an interaction between genotype and rearing experience ($F = 6.68$, $p = .015$) but no main effects (Figure 4). Mother-reared male monkeys with the low-activity allele spent more time engaged in aggressive behavior (mean sec = 259.6 ± 54.6) than nursery-reared male monkeys with the low-activity allele (mean sec = 65.9 ± 44.6) and mother-reared male monkeys with the high-activity genotype (mean sec = 66.0 ± 69.0). In both tests, the higher standard error around the mean for mother-reared male monkeys with the low-activity MAOA allele and peer-reared male monkeys with high-activity alleles was due to two outliers. Analyses conducted without the outliers did not significantly alter the statistical findings. We also conducted a power analysis to ensure that our sample size was adequate for this study. Given our data set, we estimated the power to detect the interaction effects at .74 for competitive aggression and .79 for home cage aggression.

Discussion

Our results provide evidence of an association between variation in the rhMAOA-LPR and aggressive behavior in male rhesus monkeys that is dependent on early environment; how-

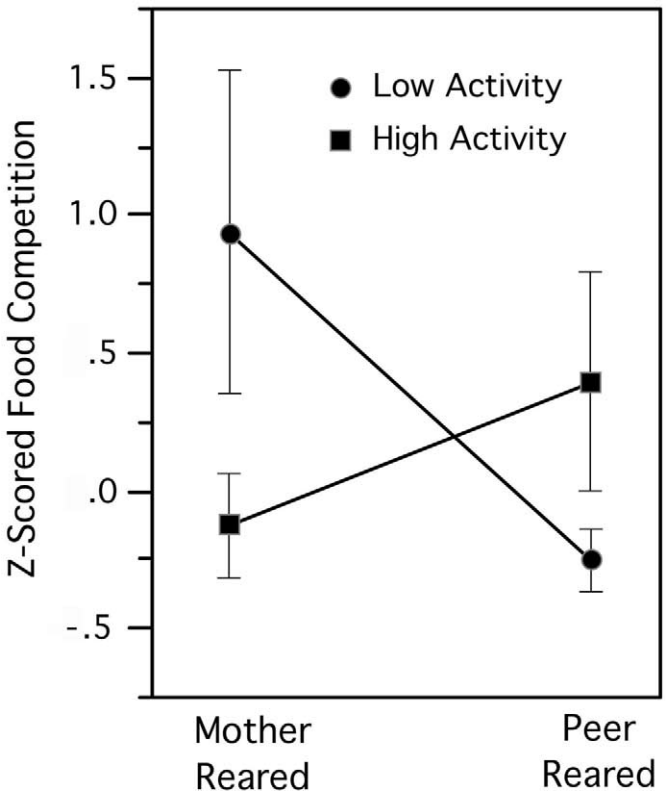

Figure 3. Effects of rhMAOA-LPR high-activity (5- and 6-repeat) and low-activity (7-repeat) genotypes and early rearing environment (mother-reared vs. peer-reared) on aggressive behavior during food competition. Data were available for 34 subjects: 22 peer-reared (high activity, $n = 10$; low activity, $n = 12$) and 12 mother-reared (high activity, $n = 5$; low activity, $n = 7$). For analysis, raw values were transformed to standard scores for each individual within its birth cohort. Results are shown as means ± SE. Analysis of variance yielded no main effects for rhMAOA-LPR or rearing environment but did indicate a significant interaction between rearing environment and genotype on competitive aggression [$F(1,30) = 5.43$, $p = .03$]. Post hoc tests (Fisher's protected least significant difference, $p < .05$) indicated that aggressive behavior was significantly influenced by genotype for mother-reared but not peer-reared subjects, such that low-activity mother-reared subjects had higher competitive aggressive behavior than their high-activity counterparts and low-activity peer-reared monkeys. rhMAOA-LPR, rhesus monkey monoamine oxidase A gene-linked polymorphic region.

ever, we found that neither genotype nor early rearing experience alone were sufficient to influence statistically meaningful differences in aggressive behavior in our test subjects. Male monkeys that engaged in competitive aggression most frequently, measured during dyadic food competition as well as in normal social group settings, carried the low-activity rhMAOA-LPR allele but were raised with their mothers in typical age-varied social groups rather than in peer-only groups.

In our colony, monkeys reared without their parents consistently show altered behavior, including increased aggression, and it is abundantly clear that parental absence during infancy has life-long consequences on the development of competent social functioning (Bastian et al 2003; Suomi et al 1976). We had anticipated that the effects of impoverished infancy induced through parental absence would interact with low MAOA activity to increase adult aggression, as suggested by the results of similar analyses in human subjects (Caspi et al 2002; Foley et al 2004). Yet the peer-reared male monkeys with low MAOA activity engaged in the least amount of competitive and social group aggression and were essentially undifferentiated from mother-reared male monkeys with the high-activity alleles. For the mother-reared monkeys, our findings are consistent with some of the human and rodent studies that associate greater aggression with genetic deficiencies in MAOA (Brunner et al 1993; Cases et al 1995), yet are in contrast to studies demonstrating the compounded risk for high aggression in individuals with both the low-activity genotype and childhood maltreatment (Capsi et al 2002; Foley et al 2004).

There are several potential explanations for our findings. First, the childhood maltreatment experienced by human subjects in the Caspi and Foley studies primarily took the form of abuse and aggression by adults, whereas the adversity modeled in our rhesus monkeys is characterized by complete absence of adult interactions and limited experience with models for aggression or violence during the early developmental period. Second, species differences in the role of aggression and its social context must also be considered. For rhesus monkeys, the development and expression of competence in aggressive behavior is critical to social success and survival. It is important to note that much of the aggression measured during food competition and in social groups should be regarded as falling within the range of normal

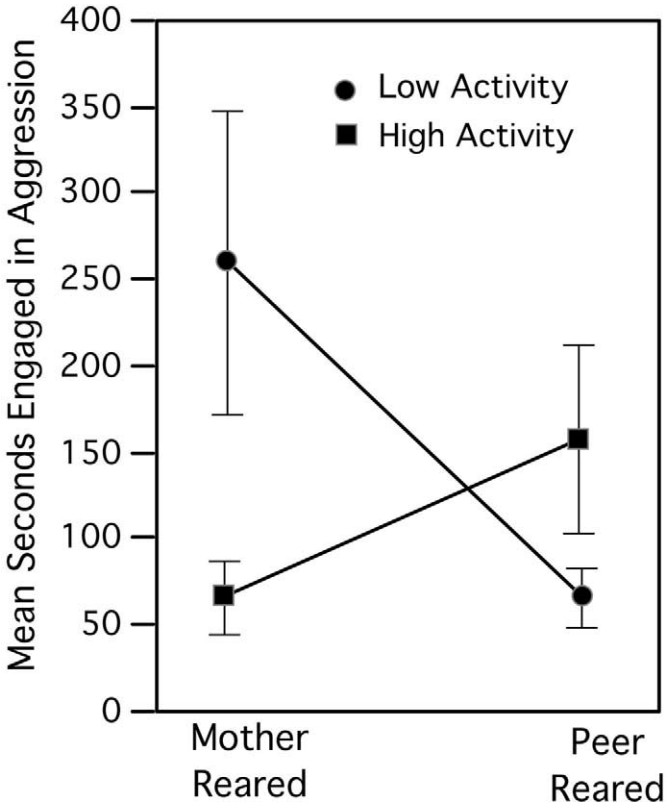

Figure 4. Naturally occurring aggression during daily social interactions, shown as a function of rhMAOA-LPR and early rearing environment. Data were available for 35 subjects: 22 peer-reared (high activity, $n = 10$; low activity, $n = 12$) and 13 mother-reared (high activity, $n = 5$; low activity, $n = 9$). Analysis of variance yielded no main effects of rhMAOA-LPR genotype or rearing environment but did reveal a significant interaction effect between genotype and rearing [$F(1,31) = 6.68$, $p = .02$]. Post hoc tests indicated that mother-reared male monkeys with the low activity–associated rhMAOA-LPR allele spent more time engaged in aggressive behavior than their high-activity counterparts, as well as the peer-reared subjects with either allele. rhMAOA-LPR, rhesus monkey monoamine oxidase A gene-linked polymorphic region.

social behavior (i.e., it is not necessarily antisocial behavior). It is reasonable to suggest, then, that the form of increased aggression that does not escalate to injurious levels, which is more common among peer-reared subjects, might be advantageous for male rhesus monkeys, and that the low-activity MAOA allele might be under positive selection. This is supported by our observation (unpublished) that male monkeys with the low-activity MAOA allele attain higher dominance rank in our colony. Third, MAOA-deficient mice are reported to show increased reactivity to stress (Cases et al 1995), suggesting, perhaps, a similar response in monkeys with low MAOA activity that might compound observed increases in stress-reactivity evidenced by peer-reared subjects (Suomi 1991). This might result in increased inhibition that, in turn, would manifest as decreased participation in social activity, including aggressiveness. Indeed, studies show that nursery-reared monkeys are prone to developing fearful and anxious temperaments (Higley and Suomi 1986).

Similar to findings from human cohorts, aggressive behavior in monkeys is increased in the presence of both low MAOA enzymatic activity as well as early exposure to a range of social behaviors that includes adult aggression. Taken together, these results lend additional support to the observation that genetic susceptibility or vulnerability depends critically on environmental modulation. Because rhesus monkeys exhibit temperamental and behavioral traits that parallel human behaviors associated with allelic variation of MAOA function, it might be possible to better understand the proximal and ultimate mechanisms producing individual differences in such traits. Nonhuman primate studies investigating the genotypic × environmental interaction in social functioning might also be useful in identifying environmental factors that either compound the vulnerability conferred by a specific genetic mutation or, conversely, act to improve the behavioral outcome associated with that genotype. In turn, the similarity of both genomic and behavioral variation in humans and rhesus monkeys indicates the potential value of nonhuman primate models in determining whether MAOA gene variation might be used to better target therapeutic agents and protective experiential therapies used in the treatment of aggressive and violent behavioral disorders.

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