

The importance of stress and genetic variation in human aggression

Ian W. Craig

Summary

Both genetic and environmental factors have key roles in determining aggressive tendencies. In particular, reaction to stress appears to be an important factor in precipitating aggressive episodes and individuals may vary in their ability to cope with stressful environments depending on their genetic make up. Evidence from humans and primates indicates that adverse rearing conditions may interact with variants in stress and neurotransmitter pathway genes leading to antisocial and/or violent behaviour. Common alleles of some serotonin pathway genes, including those involved in its degradation (monoamine oxidase A, MAOA), or its reuptake into pre-synaptic neurones (serotonin transporter, SERT) have been shown to confer functional variation. Examination of the interaction between the alleles of such polymorphisms (in particular those affecting MAOA) and environmental stressors suggest that they may provide protection against, or increase sensitivity to, abusive upbringing; an observation that may explain part of the variability in developmental outcomes associated with maltreatment. *BioEssays* 29:227–236, 2007.

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The “cycle of violence”

It has become increasingly recognised that, in an analogous manner to the ancient observation by Plutarch that one drunkard begets another “Ebrii gignunt ebrios,” there exists a pattern in human society in which children from abusive family backgrounds have increased risk of exhibiting antisocial

behaviour (ASB) and becoming poor parents in their turn, in the so-called “cycle of violence.”^(1–3) This essay explores the possible links between the stresses resulting from the experience of an abusive childhood and the individual differences in genetic background that may lead to antisocial or violent behaviour.

Any evaluation of this sort has to be considered in the context that males are overwhelmingly responsible for physical acts of violence in society. For example, crime statistics from the USA show males to be 10 times more likely than females to commit murder and more than 5 times as likely to be under ‘correctional supervision’ for criminal offences (see <http://www.ojp.usdoj.gov/bjs/>). Similarly, in a longitudinal study of about 1,000 individuals over the period from three to 21 years, males were found to be 2.4 times more likely to be involved in antisocial behaviour than females.⁽⁴⁾ Therefore, any genetic or physiological hypothesis attempting to explain the factors underlying the cycle of violence must accommodate the obvious sex differences in behavioural patterns. Furthermore, it is inescapable that hormones have profound effects on developmental differences between the sexes, including that of the brain e.g. see Craig et al.⁽⁵⁾ Animal studies indicate that testosterone levels appear strongly to influence aggression. The situation in humans is, however, not so clear and there are reports both supporting and failing to support a significant role for testosterone levels in contributing to violence and antisocial behaviour.⁽⁵⁾ While it could be postulated that a link between abusive environments and violence mediated through changes in testosterone levels might exist, a direct relationship of this sort is unproven. An alternative starting point for an investigation into the “cycle of violence” is to develop a better understanding of the physiological responses to stressful conditions and the genetic factors that modulate their impact.

Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London PO82, De Crespigny Park, London SE5 8AF, UK. E-mail: i.craig@iop.kcl.ac.uk
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Abbreviations: MAO, monoamine oxidase; SERT, serotonin transporter; 5-HT, serotonin; ASB, antisocial behaviour; HIAA, 5-hydroxyindoleacetic acid; CRH, corticotrophin-releasing hormone (previously known as corticotrophin-releasing factor, CRF); CSF, cerebral spinal fluid; GR, glucocorticoid receptor.

The role of stress in the aetiology of human aggression

Both environmental and genetic factors may influence exposure to stressful life events;^(6–8) nevertheless, there is general agreement that stress in early life can lead to violence and antisocial outcomes later. For example, key findings from

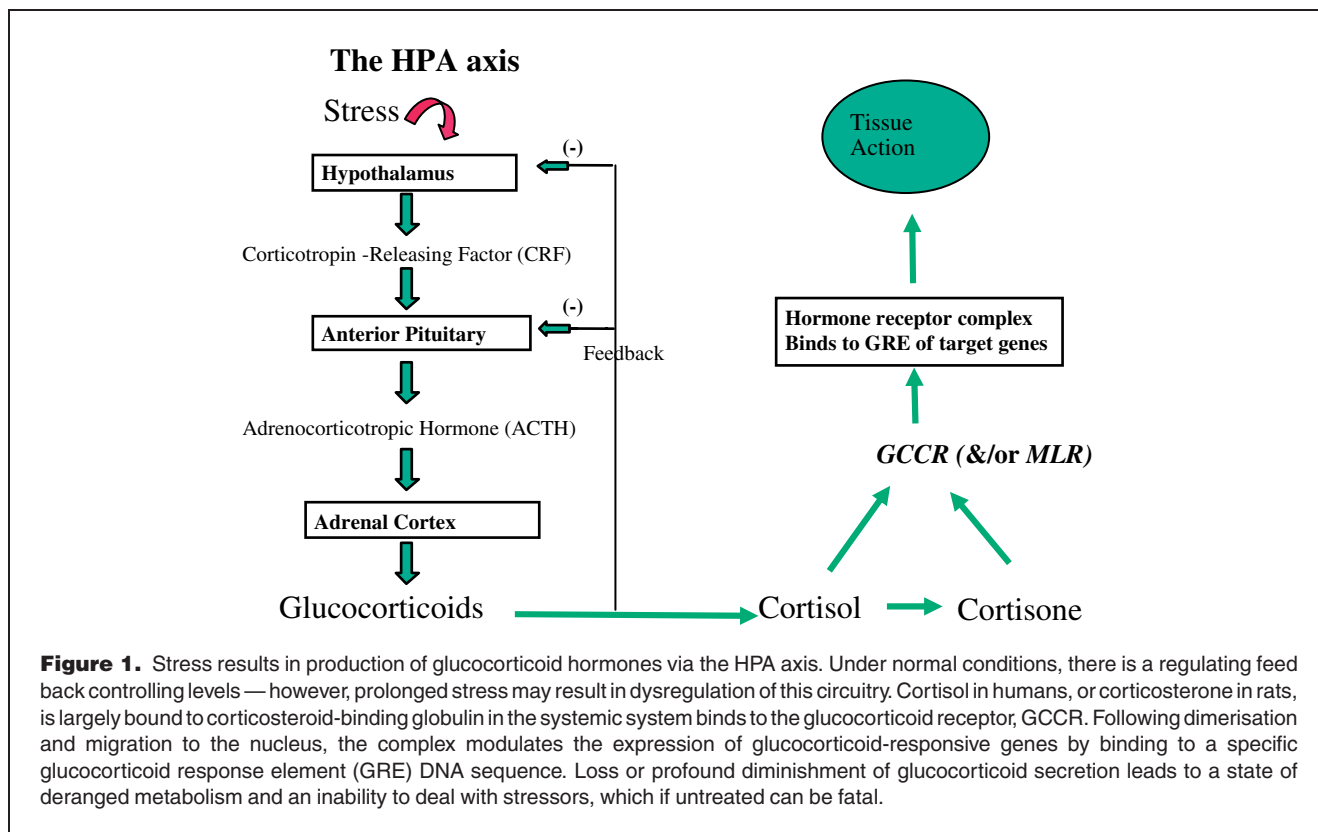
one of the most-comprehensive studies, which compared 908 cases of well-authenticated childhood maltreatment with 667 matched controls, showed physical abuse and neglect to increase the likelihood of arrest as a juvenile by 59% and as an adult by 28%. The increase for crimes of violence was 30%. (US Dept of Justice <http://www.ncjrs.org/pdffiles1/nij/184894.pdf>). While there were interesting differences when the results were classified by race or by sex and there have been many other studies differing in detail, there is little overall departure from the main result that maltreatment and neglect (both strong chronic inducers of stress) in childhood leads in turn to a substantial increased risk of violent offences and/or the development of abusive parenting styles.

Our overall understanding of the stress response implicates primary roles for the hypothalamus, pituitary and adrenal glands, the HPA axis. The genes implicated in the complex interactions leading to a behavioural response can be divided into two broad categories, those encoding the autonomic reaction to stressful situations and those involved in the neuroendocrine stress response.

Initial reactions to stress are typically those of “fight or flight” and are mostly mediated by sympathetic nervous system and the release of epinephrine from the adrenal medulla. The inclusion of the “fight” element in this classic duality is an obvious recognition of the potential violent response that stress can engender.

A more-delayed response is initiated by neural signals to the hypothalamus, which results in the release of corticotropin-releasing hormone (CRH) stimulating the release of adrenocorticotrophic hormone, ACTH, from the anterior pituitary and thereby signalling cortisol production by the adrenal cortex. Production of cortisol assists in restoring homeostasis in response to stress; however, prolonged exposure can be potentially harmful. Overall, the HPA axis exhibits three prominent features that interact to alter regulation of ACTH and corticosteroid secretion. These are a circadian rhythm in basal activity, a feedback mechanism moderated by corticosteroids and, finally, differences in response to acute and to chronic stress (see Fig. 1).

Reactions to acute stress are usually accompanied by perturbations of serotonergic activity indicated by altered levels of serotonin in nerve synapses, or its metabolites, in cerebrospinal fluid, CSF. At the presynaptic level, numerous stressors increase nerve firing and release of extracellular serotonin in nerve terminals.⁽⁹⁾ The serotonin transporter (variously referred to as HTT, 5-HTT or SCL6A4 and, hereafter as SERT), which takes up serotonin following its release into the synaptic cleft, plays a pivotal role in brain serotonin homeostasis (see Fig. 2). It is also the initial target for both antidepressant drugs and drugs of abuse, some of which are potent neurotoxins. In order to relate these features of stress to the manifestation of ASB and given the greater tractability



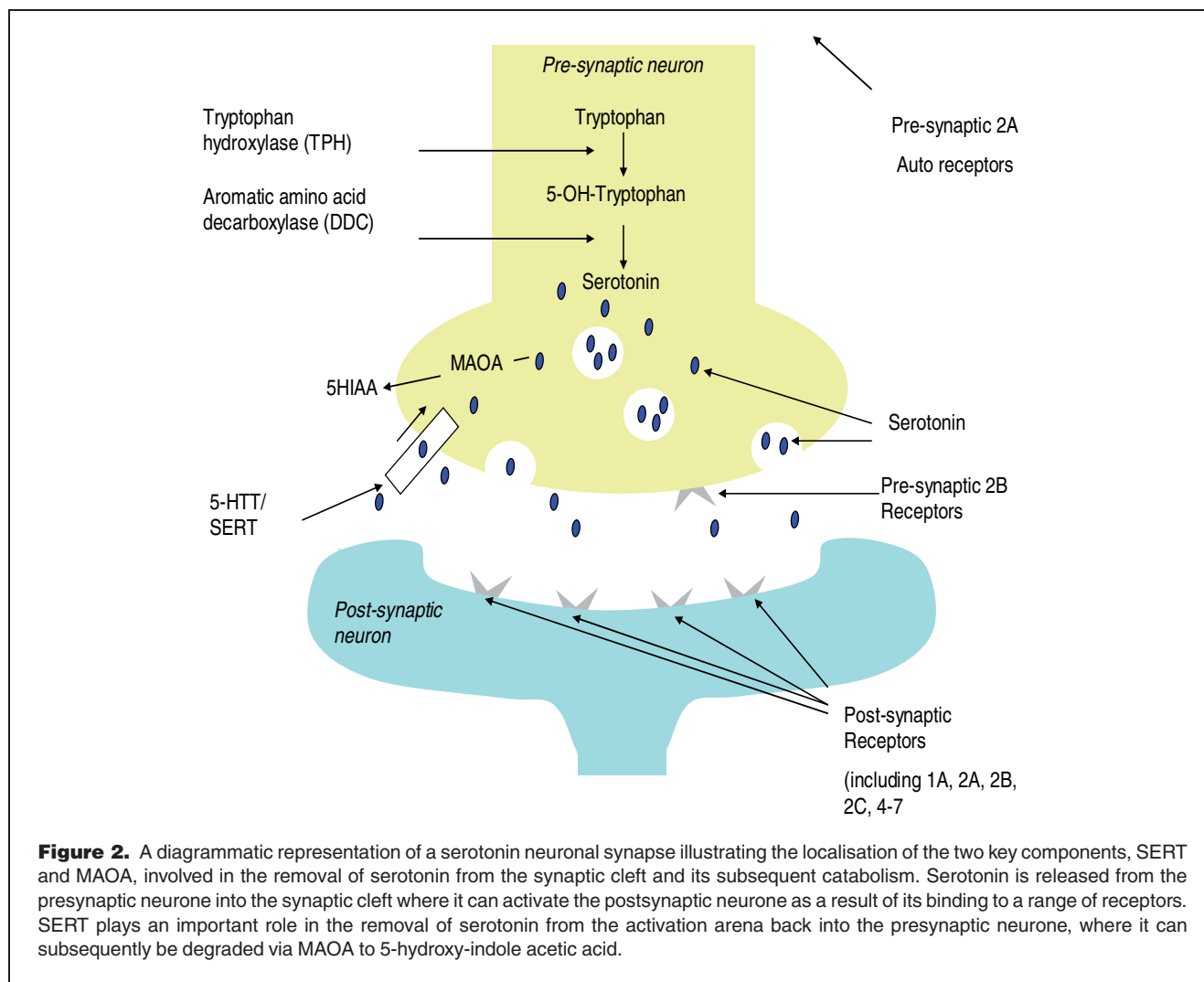


Figure 2. A diagrammatic representation of a serotonin neuronal synapse illustrating the localisation of the two key components, SERT and MAOA, involved in the removal of serotonin from the synaptic cleft and its subsequent catabolism. Serotonin is released from the presynaptic neurone into the synaptic cleft where it can activate the postsynaptic neurone as a result of its binding to a range of receptors. SERT plays an important role in the removal of serotonin from the activation arena back into the presynaptic neurone, where it can subsequently be degraded via MAOA to 5-hydroxy-indole acetic acid.

of non-human models in studying the effects of adverse environments, an obvious starting point is to consider the evidence linking stress response and aggression in animals.

Influence of early maltreatment on aggression outcomes in animals

Exact parallels between the patterns of stress experiences in humans and experimental animals are not easy to establish. In particular, the precise timings and combinations of emotional, psychological and physical abuse to which humans may be exposed are difficult to recapitulate in animals and conclusions based on non-human studies are obviously limited in their direct relevance. Nevertheless, useful examples of stress response have been based on the resident/intruder and repeated social defeat paradigms in rodents and on comparisons between peer-raised and maternally raised rhesus macaque monkeys. Both of these provide plausible models that may have some resonance in the human situation.

Stress, the HPA axis and serotonin metabolism in rodents

A recent review has summarised the long-term behavioural and physiological consequences in rodents of short-lasting stressors.⁽¹⁰⁾ It appears that significant and long-lasting changes in both behaviour and neuroendocrine function can result from exposure to short-lasting stress encounters such as foot shocks and restraint [see Refs. 11,12]. Furthermore, it appears that these longer-term effects may be mediated through enhanced HPA axis functioning⁽¹³⁾ and a decrease in the ratio between mineralo- and gluco-corticoid receptors.⁽¹⁴⁾

The social defeat model is typified by exposure of a male rodent to a superior aggressive male of the same species, where, typically, the resulting stress leads to both acute and long-term behavioural and physiological changes accompanied by significant brain neurochemical alterations. The timing and persistence of the effects may alter depending

on the precise patterns of stress and the measures analysed; but the overall picture remains much the same.^(15–17)

Recent studies on rats indicate that a rapid positive feedback exists in which a social challenge, or stressors unrelated to aggression, can activate the HPA axis leading to an acute increase in glucocorticoids, which in turn increases sensitivity to aggression promoting stimuli that further activate the hypothalamic attack area leading to further activation of the HPA axis. Thus, a vicious circle of endocrinological events leads to an uncontrolled escalation in violent behaviour.⁽¹⁸⁾

With regard to the effects on the HPA axis, it has been established that maltreatment of rats in early life results in exaggerated stress response in adults and induces hypersensitivity to glucocorticoids together with decreasing the later ability of the hippocampus to respond to stress.^(19,20) In addition, the major neurotransmitter systems, including those based on norepinephrine, serotonin and dopamine show substantial alterations (usually hyperactivation). Further evidence of changes to the serotonin system is provided by variable alterations in the concentration of the HTR1A autoreceptor (see Fig. 2) with animals exposed to stress having decreases in HTR1A mRNA levels and receptor density (e.g. see Ref. 21).

An intriguing additional level of complexity has now been encountered through the observation that maternal behaviour in rats may epigenetically modify (through methylation) the activity of their pups' glucocorticoid receptor gene. Early, deficient maternal care (presumably highly stressful to the pups) results in extensive methylation and thereby impacts on the HPA axis through reduced GR expression, which may in turn lead to atypical behaviours including impaired mothering in the daughters.⁽²²⁾

Given the importance in stress and aggression of serotonin metabolism, there are relatively few observations on the response of the major enzyme involved in its breakdown (monoamine oxidase A, MAOA) to stressful environments in rodents. It has been reported, however, that acute emotional stress and social subordination modulate MAOA and MAOAB activities in a variety of brain areas.^(23,24) Possibly of more direct relevance to studies on the “cycle of violence” is the evidence that social stress and defeats in aggressive confrontations have a direct effect by increasing transcription of both MAOA and SERT in the brain of CBA/Lac male mice.⁽²⁵⁾ This may reflect a compensatory response to activation of the serotonergic system stimulated by the social stress.

Overall, the data from rodents suggest that stress engenders mechanisms implicating the HPA axis and serotonin turnover, which have important short-term behavioural effects, but which also have homeostatic consequences attempting to protect against longer term damaging outcomes. Repeated acute or chronic stress may irreparably damage the normal flexibility of this balance with disturbed behavioural consequences. For a further evaluation of the contributions of

aggression studies on the pivotal genes in the serotonin system in experimental animals and a reminder of the complexities of the pathways involved, as evidenced by somewhat discrepant conclusions on the significance of serotonin levels resulting from comparative studies on mice and rats, the reader is referred to the recent review by Popova.⁽²⁶⁾

Non-human primates

Because of their close genetic identity, non-human primates are a valuable source of information on possible gene—environment interactions in human behaviours. Early studies on rhesus macaques suggested that stress, resulting from maltreatment in early life, can result in long-term alterations to the norepinephrine, serotonin and dopamine neurotransmitter systems thereby influencing adult behaviours.⁽²⁷⁾ In a fascinating series of observations extending over the last decade, it appears that there are marked divisions among rhesus macaque monkeys in their response to early environmental stress centred on the key serotonin metabolising enzymes SERT and MAOA. A small proportion of macaques raised in the wild, exhibit atypical impulsive and aggressive behaviour in response to stressors which appears to correlate with long-term deficits in their serotonin metabolism. A similar pattern is observed for a minority of captive populations and this subgroup, characterised by excessive impulsivity and by making severe and inappropriate attacks on others, have remarkably low CSF levels of the serotonin metabolite 5-hydroxyindole acetic acid, HIAA, which is produced by the action of MAOA (see Fig. 2). This characteristic, which can be observed as early as 14 days, may persist during development up to 4 years, and, although strongly heritable, is also highly dependent on environmental influences relating to stress and adverse conditions.

Rhesus monkeys raised for the first six months in a peer group and separated from their mothers typically have lower HIAA levels in the CSF than their maternally raised equivalents and show higher rates of impulsive aggression. Intriguingly, the pattern of low levels of HIAA also appears to reflect an interaction with a polymorphism in the promoter of the serotonin transporter gene. This, like its human counterpart, has two major alleles distinguished by a repeat in the promoter region. The version with a longer repeat (*l*) provides higher transcription levels than the short version (*s*) and *l/l* homozygous individuals are presumed to provide higher levels of the transporter at synapses than the *l/s* heterozygotes and hence clear released serotonin more efficiently (*s/s* homozygotes are too infrequent to provide useful data). Nevertheless, in spite of a reduced capacity in this respect, heterozygous monkeys given a less stressful upbringing, as a result of being raised by their biological mothers, show resilience in maintaining normal levels of CSF HIAA. These are significantly higher than the levels observed for their heterozygous, peer-reared counterparts.⁽²⁸⁾ Relative genetic deficiencies in the serotonin system

as manifest by the (*l/s*) heterozygotes appear therefore to sensitise the animals to the stress of maternal deprivation with consequent increased aggressive outcomes.⁽²⁹⁾

Influence of early maltreatment on aggression outcomes in humans

It is first worth noting that individuals do not experience stressful life events at random. There are significant genetic influences on perception and experience of negative life events accounting for about 40% of the variance in the reports of such events remembered in later life.⁽⁶⁾ Keiley et al.⁽³⁰⁾ observed that the earlier children were exposed to harsh treatment, the more likely they were to manifest adjustment difficulties in early adolescence and teachers' reports confirm that those with early abuse show the highest scores for ASB over the kindergarten period (controlled for socio-economic status and gender).

Patterns of neuroendocrine response to stress in humans

Information concerning the physiology of the stress response in humans indicates that, in general, the same neuroendocrine players are involved and that some of the symptoms seen in humans reacting to stress resemble those seen in other animals [see Ref. 12]. Unfortunately, in spite of the wealth of information concerning the role of variation in the genes controlling key steps in the HPA axis, there is little information on how these moderate the relationship between stress and ASB.⁽³¹⁾ However, in light of the perceived importance of the serotonin system in aggression generally, and its intriguing role in rhesus monkeys in particular, it is interesting to attempt to assess the role of genetic variation in serotonin-metabolising enzymes SERT and MAOA and the interaction of such variation with stressful environments in humans (e.g. see Ref. 32). While a considerable body of research indicates that initial responses to stress result in increased serotonin synthesis and turnover, it is also well established that, in the long term, there are low levels of the serotonin metabolite, HIAA, in the cerebrospinal fluid of individuals manifesting persistent impulsive, externally directed aggression. These features may also be linked with a history of alcohol and substance abuse and mild hypoglycaemia. These comorbid attributes have been proposed by Linnoila to comprise a "low serotonin syndrome"^(33,34) and have resonance with the related theories of the hypoglycaemia–aggression hypothesis. There is also evidence that altered norepinephrine and serotonin levels are linked to delinquency and violence and that maltreatment in childhood has lasting neurochemical correlates⁽³⁵⁾ and see Ref. 3. Furthermore, evidence suggests that there are reduced levels of both serotonin and its metabolite HIAA in post-mortem brains of depressed patients who have frequently experienced long-term stressful environments.⁽³⁶⁾ At the genome level, there are reports of a significantly reduced

frequency of the 10R allele of a variable repeat motif located in the second intron of the *SERT* gene with persistent and pervasive aggressive behaviour in children.⁽³⁷⁾ This association is of interest because the 10R allele is of putatively low activity compared with other major alleles tested.

Attempts have been made to relate stress changes in the HPA axis to the response of the serotonin system and possible clues as to how this may occur has emerged from the demonstration that increasing levels of a potent glucocorticoid analogue (dexamethasone) produced a specific dose response from the promoter driving the transcription of the *SERT* gene *in vitro*⁽³⁸⁾ coupled with the observation that the *MAOA* gene also has glucocorticoid response elements in its promoter region that regulate expression in cultured cells.⁽³⁹⁾

Such, essentially indirect, observations have now been complemented by direct scanning of brain activity and chemistry, which has enabled examination of the SERT distribution in the brains of individuals with impulsive aggressivity. For example, Frankle et al.⁽⁴⁰⁾ employing positron emission tomography, showed that SERT availability was reduced in the anterior cingulate cortex of impulsive-aggressive individuals compared to healthy control subjects.

Finally, there have been many attempts to discover possible roles in aggression of genetic variants in other components of the serotonin pathway including the serotonin receptors, with some positive findings. Variation in the genes for both HTR1A and HTR1B have been variously implicated as potentially linked to impulsivity, antisocial personality and conduct disorder.^(41,42)

MAOA as a candidate gene for antisocial and other behavioural disorders in humans

As indicated previously, there are two forms of monoamine oxidase enzymes in humans. MAOA and MAOB are encoded by separate, but highly homologous X-linked genes, oriented in an adjacent, tail-to-tail (3'–3') fashion. Both are expressed in most brain areas with some regional variation and also in a variety of other tissues. It is generally considered that MAOB has an additional wider role in metabolising dietary amines. Interestingly, *MAOB* transcripts appear at highly elevated levels in the amygdala, prefrontal cortex and hypothalamus (<http://expression.gnf.org/>). Notwithstanding the existence of two forms of the enzyme and perhaps short-sightedly, most behavioural studies have concentrated on the A form. The main role of MAOA is thought to be in degrading serotonin following its re-uptake by the serotonin transporter from the synaptic cleft; although it is also capable of degrading both norepinephrine and dopamine. It therefore plays a key role in the regulation of synaptic activity and alterations in its activity produced by pharmacological intervention, or through genetic variants, are likely to have profound effects on behaviour as evidenced by the use of MAOA inhibitors in the treatment of behavioural disorders, including depression.

Variants associated with altered expression/activity of MAOA

In the recent past, a variety of SNPs and variable copy number repeats have been detected in and around *MAOA*.^(43–45) These have provided a basis for association studies, some of which yielded positive associations with aggressive behaviours (e.g. see Table 1). Of particular significance was the subsequent recognition of a novel motif localised 1.2 kb upstream from the *MAOA*-coding region, comprising a 30 bp repeat existing in 3, 3.5, 4 or 5 copies⁽⁵⁴⁾ in a region identified as a promoter.⁽⁵⁵⁾ It was noted that, as in all subsequent publications, the two major alleles seen were those with 3 or 4 copies of the 30 bp sequence. Of fundamental importance, was the demonstration that the copy number had a significant effect on the level of expression in transfection studies and cultured fibroblasts with the 3 repeat allele supporting only reduced transcription compared with longer repeat number alleles.^(54,56,57) Brain imaging studies, however, have been less conclusive.^(58,59) Sabol et al.⁽⁵⁴⁾ also reported significant variations in the distribution of the repeat alleles among major population groups, suggesting that population stratification could be a major confound in the interpretations of association studies, an observation not always taken into consideration in subsequent studies.

MAOA variants and antisocial/aggressive behaviours

A watershed concerning the potential role for *MAOA* variants in the aetiology of ASB and conduct disorders at the population level was the report of Brunner et al., in 1993, who described the segregation in males from a Dutch pedigree of a complex behavioural syndrome (including impulsive aggression and

dysfunctional sexual attitudes) with a nonsense mutation resulting in zero activity of the enzyme.⁽⁶⁰⁾ Apart from some males with deletions covering the Norrie disease gene and the adjacent monoamine oxidase A and B loci, this has been the only report of the phenotypic consequences of a null mutation at this locus.⁽⁶¹⁾ The complex phenotype of Norrie disease including blindness and, in some cases, sensorineural deafness makes any assessment of the contribution of *MAOA* and *MAOB* genes to impulsive aggression difficult. A role for *MAOA* deficiency in promoting aggression, however, is further strongly supported by studies on transgenic mice that have a 17 kb deletion embracing exons 2 and 3 of the *MAOA* gene (as the result of an unplanned, but successful gene knock-out). This effectively abolished enzyme activity in brain and liver.⁽⁶²⁾ Behavioural studies on the adult males indicated heightened aggression in resident–intruder tests and also increased inappropriate grasping during courtship.

Since this time, several reports have suggested that less dramatic variation at the *MAOA* locus may be implicated in the aetiology of human aggression and/or ASB in males (see Table 1). This also includes information on the impact of *MAOA* variants on aggression associated with alcohol addiction and with attention deficit and hyperactivity syndrome, ADHD, as the latter is increasingly being recognized as a potential precursor to antisocial behaviour in adults. Other studies, however, have been unable to confirm various elements in this pattern of observations.^(63–65) Furthermore, more relevant to studies on aggression, Manuck et al, in an investigation of inter-individual variability, found males with the low-activity allele showed less, rather than more, dispositional aggressiveness, impulsivity and central-nervous-system serotonergic responsiveness.⁽⁶⁶⁾ Similarly, psychiatrically referred

Table 1. Selected positive associations of MAOA variants with phenotypes relating to violence and antisocial behaviour—excluding those for which an interaction with the environment (e.g. childhood abuse) has been examined

| Marker | Population | Associated phenotype | P value | Reference |
|---|-----------------------|--|--------------------------|-----------|
| Intron 2 microsatellite—longer alleles | Adolescents-Caucasian | Conduct disorder | Trend | (46) |
| <i>EcoRV</i> RFLP Also intron 2 microsatellite allele 6 | Han Chinese | Susceptibility to alcoholism | $P = 0.02$; $P = 0.005$ | (47) |
| Promoter VNTR Low activity allele(s) | United Kingdom | Male ADHD probands | $p = 0.025$ | (48) |
| Haplotype with promoter VNTR Low activity allele(s) | Irish | Comorbid conduct disorder | $p = 0.08$ in TDT | (49) |
| Promoter VNTR Low activity allele(s) | Finnish | Male ADHD probands | $p = 0.05$ in TDT | (49) |
| Promoter VNTR Low activity allele(s) | Finnish | Male type 2 alcoholics (with antisocial behaviour); Not type 1 (i.e. without antisocial behaviour) | Trend | (50) |
| Promoter VNTR Low activity allele(s) | German | Antisocial alcoholics compared with those exhibiting anxious-depressive symptoms | $P = 0.02$ | (51) |
| Promoter VNTR Low activity allele(s) | German descent | Male type 2 alcoholics (with antisocial behaviour) | $p = 0.008$ | (52) |
| Promoter VNTR Low activity allele(s) | European descent | Male type 2 alcoholics (with antisocial behaviour) | $P = 0.02$ | (53) |

Note: Direct evidence of functionality has not been demonstrated for any of the markers apart from the promoter polymorphism. As considerable LD exists across the locus, it is probable that associations noted for other MAOA markers reflect proximity of the promoter. VNTR. It also should be noted that there has undoubtedly been a bias in the reporting of positive findings.

male children with persistently associated aggressive behaviour have been found to be significantly more likely to carry the long (high-activity) allele than normal controls.⁽⁶⁷⁾ Nevertheless, overall, there does seem to be an accumulation of evidence suggesting possible association of *MAOA* low-activity variants with externalising symptoms, particularly antisocial behaviour and violence in males. Quite why this has been so difficult to observe consistently is considered in a later section.

In contrast to the studies linking violence/ASB and other externalising behaviours with the low-activity *MAOA* variants, there is intriguing evidence for an inverse pattern to this, with internalising behaviours, including anxiety, neuroticism and panic disorder apparently showing association with the high-activity allele(s).^(56,68–70) Again, as with many candidate gene studies, there is frequently a failure to replicate some of the original suggestive data. This is, of course, to be expected given the heterogeneity in the studies with respect to diagnosis and ethnicity. Similarly, failure to replicate is often a consequence of insufficient power. Apart from this, one of the main confounds of association studies is the difficulty in controlling for the environmental effects. It is probably for these reasons that the most compelling evidence concerning a role of the *MAOA*-activity variants in the aetiology of ASB in males has come from studies that included the control of significant environmental variants.

In the first of these, the role of *MAOA* was analysed in depth by investigating the variability in antisocial outcomes in male children who are maltreated.⁽³⁾ Independent source information was used to evaluate convictions for violent crimes, a personal disposition toward violence, symptoms of antisocial personality disorder at age 26 and adolescent conduct disorder (assessed according to DSM-IV criteria). Whichever of these measures was examined, an association between maltreatment and antisocial behaviour conditional on the individuals *MAOA* genotype was observed with those carrying the low-activity allele being at the greater risk; although mere possession of the low-activity allele itself was not a predictor of aggression. In contrast, possession of high-activity alleles in males who had been subjected to maltreatment appeared to confer protection against the later development of antisocial behaviour. This study also showed that there was no significant association of an individual's *MAOA* genotype with their assignment to a particular maltreatment category; i.e. *MAOA* status did not appear to influence how parents treated their child.

Since this report, there have been several studies attempting to replicate the observed interaction between genotype and early maltreatment in predisposing ASB. In the first of these, individuals with relevant data were selected from 514 white male twins from the community based, longitudinal Virginia Twin Study for Adolescent Behavioural Development.⁽⁷¹⁾ Individuals were between 8 and 17 years at the time

of entry into the study. Although the measures for childhood maltreatment differed from those employed by Caspi et al.,⁽³⁾ a highly significant increase in conduct disorder with increased exposure to childhood adversities was observed for males with low-activity *MAOA* genotype. Males with high-activity alleles were much less likely to be affected.

While subsequent studies have been generally supportive of a role for *MAOA* variants in ASB and for an interaction with stressful upbringing,^(72,73) Young et al.⁽⁷⁴⁾ were unable to detect a genetic–environmental interaction with *MAOA* genotype for maltreatment. They examined a mixed sample of adolescents selected for persistent conduct and substance abuse with no control group for comparison and the study was therefore atypical in this regard. Indeed, a recent replicative study and meta-analysis of the relationship between *MAOA* genotype, maltreatment and gene by environment interaction, in predicting children's mental health, has provided strong evidence for the importance of *MAOA* genotype in influencing the vulnerability in early life to environmental stress.⁽⁷⁵⁾ These findings have important social implications, nevertheless, much more remains to be accomplished in establishing the periods of most sensitivity to abuse, the roles of other genes, their potential interactions and in refining the key stress factors. Most recently, the protective effect of the high-activity allele from an increased risk of becoming violent or antisocial in later life of abused and neglected white, but not black, individuals has been reported. Interestingly, in this study, the same direction of effect was seen for white females for juvenile but not adult behaviour.⁽⁷⁶⁾ The X-localisation of the *MAOA* gene raises several problems with studies on females. There are conflicting data concerning the X-inactivation status of *MAOA*, with the lack of reliable information on dosage effects making interpretation of actual levels of the enzyme in the different genotypic classes problematic. Resolution of these difficulties awaits further investigation of *MAOA* inactivation status in brain.

Several important points emerge from these studies. It is noteworthy that most reports failed to detect a significant main effect of the low-activity allele in predisposing aggression in the absence of environmental stress and a simplistic interpretation that *MAOA* genotype can be used as a predictor of aggressiveness in humans is untenable. A second point is that the majority of positive gene–environmental interaction findings relate to the behaviour of adolescents or relatively young adults. Much remains to be established concerning the long-term outcomes of the gene by environment interactions. Finally, although authors have tried to provide comparable measures of abuse and of antisocial behaviour and aggression, it is inevitable that differences exist that may be fundamental to the outcomes noted. Some standardisation in this regard would be valuable although difficult to achieve in practice.

It turns out that the interactions observed between *MAOA* genotype and aggression may also be a feature in related

primates. A recent exciting finding relevant to the evolutionary origins of the *MAOA* promoter polymorphism has been the discovery of a similar promoter variant system in rhesus macaques. The repeat motif is 18 base pairs long and it appears that it too can regulate the expression of *MAOA* and, fundamental to the potential role of *MAOA* in human ASB, male individuals with the lower-activity form exhibited more aggression in competing for food.⁽⁷⁷⁾

A possible link between the stress response and MAOA genes and serotonin

In trying to understand the role of *MAOA* in the “cycle of violence,” one missing link is how abuse and stress are related through the functional polymorphism to the manifestation of antisocial behaviour and aggression. It could be that the apparent risk conferred by the low-activity allele reflects a relative inability to respond to the effects of stress arising from maltreatment. Reduced ability to counter possibly detrimental increases in monoamine levels (that could result from possession of the low promoter genotype) might compromise the ability to cushion the release of excess neurotransmitter. This in turn might increase sensitivity to acute stress and result in violent outbursts and/or other aggressive outcomes.

In this context, it may be relevant that chronic emotional stress, such as that resulting from a series of defeats in rodents, is accompanied by the induction of the transcription factor *c-fos* in many brain regions of rats and mice including the dorsal and median raphe even after repeated encounters [e.g. Refs. 78,79] and that a non-threatening and stimulating early environment has the reverse effect.⁽⁸⁰⁾ Although the picture is complicated by the variable responses in different brain areas, it could be speculated that elevation of the transcription factor *c-fos* may in turn be one of the factors responsible for the upregulation of the *MAOA* and *SERT* genes observed in chronic stress.⁽²⁵⁾ To date, there have been no direct attempts to investigate this; however, a search of the *MAOA* sequence reveals a cluster of *c-fos*-binding sites (AP1) in intron 10. While the consensus-binding site for *c-fos* (GAGTCA) has an expected frequency of about 1 per 4,000 bp, this cluster of seven sites in intron 10 is compressed into a 6,700 bp segment. The possible functional significance of this feature remains to be determined, but could provide a hint as to the manner in which the coupling of stress, *MAOA* alleles and aggression occurs. Certainly, profound perturbations to expression profiles in brain are the expected sequelae following acute or chronic stress and investigations of the alterations to transcription patterns (e.g. employing microarrays) may bring an understanding of the links in this complex pathway closer. It is already obvious from studies employing RNA tagging that activation of the mineralo- and glucocorticoid receptor transcription factors in the hippocampus of rats alters the expression of up to a hundred genes.⁽⁸¹⁾

Conclusion

Clearly there is a complex interaction between response to stress and the likelihood of an aggressive or a depressive outcome. Studies on genetic variations within the serotonin system and, in particular, those concerning monoamine oxidase and the serotonin transporter have allowed tantalising glimpses of the possible neurochemistry underlying ASB. Just as there are many different manifestations of ASB there are also likely to be many overlapping and interacting transmitter and hormone linked pathways in which *MAOA* and *SERT* may be bit players. In particular, the profound consequences of *MAOA* deletions in humans and mice suggest that less dramatic functional variations of this gene are likely to have significant behavioural impacts. Finally, the recent reports that similar activity variants have been discovered in primates suggests that the *MAOA* promoter polymorphism has considerable evolutionary importance and that it may have played a significant role in the recent ancestry of humans with the consequences of this reverberating in contemporary society.

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