Are the monoamines involved in shaping conduct disorders?

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Antisocial and aggressive behaviours represent a widespread and expensive social problem. Recent research has convincingly shown that there is a strong interaction between genetic inheritance and environment for development of personality and behaviour. It appears to be common knowledge that childhood maltreatment often causes psychiatric problems (e.g. depression or anxiety) or behavioural problems (e.g. aggression or antisocial behaviour) later in life. The risk for such a development is, however, different between individuals and can to a large extent be explained by genetic factors.

The identification of neural mechanisms underlying human personality and temperament seems to be promising due to their considerable importance as highly heritable risk mediators for aggressive behaviour, criminal activity, as well as somatic and psychiatric disorders (Buckholtz et al., 2008; Buckholtz & Meyer-Lindenberg, 2008; Nilsson et al., 2006).

MAOs: key molecules for personality and behaviour

Monoamine oxidases (MAOs) are two enzymes (MAO-A and MAO-B) which inactivate the so called monoamine transmitter substances serotonin, noradrenalin and dopamine. The brain systems which utilise those transmitters are of great importance for the fine-tuning of personality traits, as well as state-dependent features such as mood, appetite, attention, etc. MAOs are present in almost all cells in the body, however, naturally, it is the activities of MAOs in the brain that are of

major interest in relation to personality and behaviour.

In association with a complete lack of MAO-A, as in mice in which the MAO-A gene has been knocked out, and in a Dutch family with a dysfunction of this gene, aggressiveness has been reported (Brunner, 1996). In the Dutch family aggressiveness was also combined with arson and cases of rape indicating a lack of impulse control. Extensive search for more families with this abnormality has, however, been negative.

Measurements of MAO activities in brain tissue, either post-mortem or using various imaging techniques, are, however, tedious and not suitable for larger samples of individuals. Furthermore, unless combined with functional tasks, as in functional Magnetic Resonance Imaging (fMRI), findings in relation to behaviour have usually not been particularly rewarding. This could possibly be explained by the fact that the majority of the enzyme is localised in glial cells, and that the population of enzyme molecules of immediate interest for monoamine inactivation is difficult to measure.

One of the MAO enzymes - the MAO-B - is localised in blood platelets and is therefore accessible for activity measurements in larger samples of individuals. MAO-B enzyme activity is highly inheritable, as shown in twin studies, and is stable in the individual during lifetime. Interestingly, decades ago low platelet MAO-B activity was shown to be associated with personality traits such as impulsiveness, monotony avoidance and aggressiveness, and, as a consequence, vulnerability for the type of alcoholism characterised by strong heritability and antisocial behaviour (type 2). While low platelet MAO-B activity thus involves a risk for the individual, it also might be associated, at the other end of the spectrum, with positive outcomes of impulsiveness and ´sensation seeking´ such as creativity and success.

Antisocial behaviour: biological factors

In some non-clinical series of individuals the association with aggressiveness or antisocial behaviour, however, becomes significant only if the interaction with the environment is considered, particularly in girls/females. Personality is, naturally, a result of the influence of a large number of genes, all of which result in the formation of their respective proteins, e.g. enzymes such as the MAOs.

Another protein of importance for the elimination of the neurotransmitter serotonin is the serotonin reuptake pump (5-HTT), which is the target for the currently most commonly used antidepressant drugs, the selective serotonin reuptake inhibitors (SSRIs). The gene producing this protein exists in variants among different individuals. Those variants are usually referred to as the short and the long variant, shown to be of importance for the risk of anxiety or depression (Harro et al., 2009). Not surprisingly, the association between platelet MAO-B activity and personality gets stronger if other independent factors affecting personality are eliminated. Thus, if only individuals carrying the short variant of the 5-HTT gene were investigated, the association between platelet MAO-B activity and behaviour became considerably strengthened, both with regard to impulsiveness in a large series of adolescents, and, in a small series of boys, with dimensional scores for ADHD.

The gene producing MAO-B also exists in variants. One variant of the gene is weakly associated with platelet MAO-B activity, but strongly interacts with poor psychosocial environment to predict antisocial behaviour, particularly in girls. An interesting question that remains to be answered is why the association between the MAO-B gene variant and antisocial behaviour was found to be considerably stronger than with the activity of platelet MAO-B.

A well-studied variant in the MAO-A gene is also associated with antisocial behaviour. Usually this association has been found only in

individuals in a poor psychosocial environment, where the gene variant associated with low activity (i.e. a low rate of synthesis of MAO-A enzyme) has been strongly linked with antisocial behaviour in males (Nilsson et al., 2007). Recent studies, however, repeatedly also found an association in girls/females, in some series of such a magnitude that MAO-A genotype alone - independently of environment - showed a significant association. Remarkably, all series showed that, in contrast to the case in males, the high-activity variant is the one associated with vulnerability for antisocial behaviour in females (Nilsson et al., 2008) (see figure 1). This is in line with a marked sex difference between the gene variants with regard to changes in blood flow in specific brain regions as a response to emotional stimuli, using fMRI, which has been shown by the group of Meyer-Lindenberg.

Genetic influences on impulsiveness and ´sensation seeking´

Our findings raise a number of questions:

- How are stable factors such as personality and temporal factors and current mood or appetite related to each other if brain serotonin activity is involved in both?
- How can platelet MAO-B activity be associated with a stable factor such as impulsiveness?

The view on the first question is that the personality, which is a life-long characteristic of the individual, is mainly a consequence of the size or capacity of the brain monoamine systems, while state-dependent factors such as mood are dependent on the current activity, large or small, in the system. It is obvious that an impulsive, ´sensation-seeking´ person, as well as a more introvert and monotony-resistant individual can be in a high or low mood, depending on the current situation.

Probably events during life development explain the associations between MAO gene variants and personality. During foetal development, high levels of serotonin have been shown to be an effective inhibitor of the growth of the serotonin system. Hence, gene variants inferring a low rate of inactivation of serotonin, especially during foetal life, will lead to a small or low-capacity brain serotonin system in the adult. Both experiments with animals, using serotonin specific neurotoxins, and studies on humans, e.g. by measuring levels of degradation products of serotonin in the cerebrospinal fluid, have shown that a reduced or low capacity of the brain serotonin system is linked to a personality characterised by impulsiveness and ´sensation seeking´. High ´sensation seeking´ in turn has been linked to increased risk for negative behavioural outcomes such as drug abuse etc. (Joseph et al., 2009).

With regard to the association between platelet MAO-B and personality, experimental results make us hypothesise that part of the explanation is to be found in the regulation of the activity of genes. Regardless of individual variants in the structure of genes, their activity is also regulated by activators or inhibitors (transcription factors), which bind to a specific part, the regulatory or promoter part, of the gene. There is reason to believe that the gene producing MAO-B and a number of genes producing proteins that constitute important parts of the brain monoamine systems are regulated by the same transcription factors.

One candidate for being such a common transcription factor is AP2ß (Nilsson et al., 2009). A low transcriptional activation of both the gene responsible for the production of platelet MAO-B and for a number of genes responsible for building up brain monoamine pathways could in this way explain how a low activity (or level) of platelet MAO-B protein is mirroring a weak or low capacity of the monoamine systems in the brain. These would in turn constitute the biological basis for personality traits such as impulsiveness and ´sensation seeking´.

Clinical implications

- Our gene-environment interaction findings, as well as those of others in this field, show a way of understanding biological mechanisms underlying the individual's degree of dependence on the environment for the development of e.g. substance abuse, antisocial behaviour, suicidal behaviour, etc.
- Thus, individuals with one set of MAO gene variants seem to be virtually independent of environment for the risk of e.g. antisocial behaviour, and in this way could explain resilience towards an unfavourable environment, while those with another set of MAO gene variants are highly dependent on psychosocial environment for behaviour.
- Another clinically important result is the finding of dramatic sex differences with regard to the direction of behaviour related to the interaction between MAO gene variants and environment.

Conclusion

Apart from psychosocial influences, biological factors have a major influence on personality traits and behaviour.

The aggregation of certain risk factors in the same individual has been shown to contribute to the development of antisocial behaviour. Research findings suggest that both the molecular and the psychosocial mechanisms underlying emotional response and antisocial behaviour may differ between males and females.

Based on gene-environment interactions, the brain monoamine systems play a crucial role in shaping personality traits and conduct disorder. The MAO genes appear to be the first genes strongly linked with either antisocial behaviour or conduct disorder.

Individuals with one set of MAO gene variants seem to be virtually independent of environment for the risk of e.g. antisocial behaviour, and in this way could explain resilience towards an unfavourable environment. In contrast, those with another set of MAO gene variants are highly dependent on psychosocial environment and have considerable vulnerability for antisocial behaviour.

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