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The role of MAO in personality and drug use

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ABSTRACT

Monoamine oxidases, both MAO-A and MAO-B, have been implicated in personality traits and complex behaviour, including drug use. Findings supporting the involvement of MAO-A and MAO-B in shaping personality and in the development of strategies of making behavioural choices come from a variety of studies that have examined either prevalence of gene variants in clinical groups or population-derived samples, estimates of enzyme activity in blood or, by positron emission tomography, in the brain and, most recently, measurement of methylation of the gene. Most of the studies converge in associating MAO-A and MAO-B with impulsive, aggressive or antisocial personality traits or behaviours, including alcohol-related problems, and for MAO-A available evidence strongly supports interaction with adverse environmental exposures in childhood. What is known about genotype effects, and on expression and activity of the enzyme in the brain and in blood has not yet been possible to unite into a mechanistic model of the role of monoamine systems, but the reason for this low degree of generalization is likely caused by the cross-sectional nature of investigation that has not incorporated the developmental effects of MAO-s in critical time windows, including the foetal period. The "risk variants" of both MAO-s appear to increase behavioural plasticity, as supportive environments may particularly well enhance the hidden potential of their carriers. Importantly, male and female brain and behaviours have been found very different with regard to MAO × life events interaction. Future studies need to take into consideration these developmental aspects and sex/gender, as well as to specify the role of different types of environmental factors.

1. Introduction

Given that MAO-A and MAO-B catalyze monoamines and that all monoamine neurotransmitters have in one way or another been implicated in multiple traits, notably aggressive behaviour (Miczek et al., 2015); it is no wonder that these enzymes have been common targets in many studies on personality and drug use. MAO-A and MAO-B each have specific preferential localization and substrate affinities, and more often than not have been addressed separately in experimental research. Nevertheless, under some conditions the function of these enzymes is likely to be additive (e.g., Bortolato et al., 2013).

MAO-A and MAO-B are encoded by separate genes that both are located on the X-chromosome, tail to tail with 24 kb apart, and many differences exist in the regulation of transcription between the genes (Shih and Chen, 2004). Localization of the MAO genes on the sex chromosome is part of the background in further discussion of the very significant differences between males and females in the association of MAO-s, personality and behaviour. Differences in transcriptional mechanisms may explain the tissue-specific expression of the isoenzymes (Shih and Chen, 2004). However, in humans, most organs express both MAO isoenzymes at some level, with the notable exception in the exclusive presence of MAO-B in platelets (O'Carroll et al., 1989). In the brain, MAO-A is most extensively expressed in dopaminergic neurons and MAO-B predominantly in serotonergic neurons (Westlund et al., 1988; Westlund, 1994). This pattern of localization is somewhat contrasting to the relative efficacy of substrate catabolism, as serotonin and noradrenaline are more effectively broken down by MAO-A and some trace amines such as phenethylamine by MAO-B, dopamine catabolism being similar with both isoenzymes or preferentially MAO-B controlled (Oreland, 1993; Oreland, 2004a,b). As it will be described in more detail below, what is known of the variants of either of the *MAOA* and *MAOB* genes does not explain well the corresponding enzyme activities in vivo. Notwithstanding this limited information on the mechanical links from inheritance to neurochemistry to behaviour, both gene variants and enzymatic activities of these isoenzymes have been strongly associated with aspects of personality and behavioural preferences, and it will be important to learn, why.

The bulk of the information on inter-individual variability in MAO-A and MAO-B describes its relationship with impulse control, and aggressive and antisocial behaviour. Much less has been possible to say on these enzymes with regard to other approaches to personality but some interesting findings remain in waiting for replication.

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2. Monoamine oxidase genotype: overall effects

Systematic review of literature has not suggested any strong relationship of variants of a single gene with personality either using models of Cloninger, Eysenck or Costa and McCrae (Balestri et al., 2014), with *MAOA* and *MAOB* being no exceptions. It can indeed be questioned whether such associations with common gene variants are possible to be found in principle because of the enormous selection pressure that goes against less favourable traits. Nevertheless, the *MAOA* gene offers an illuminating example of a minor variation in DNA being strongly associated with specific behavioural phenotype. Han Brunner and coworkers published in 1993 a highly influential case of a Dutch family with a point mutation that rendered the *MAOA* dysfunctional: male subjects who had the mutation and no MAO enzymatic activity exhibited markedly higher urinary 5-HT levels, borderline mental retardation, impaired impulse control and predisposition to violent outbursts in response to unexpected and stressful stimuli (Brunner et al., 1993).

2.1. MAOA

2.1.1. MAOA and personality, with focus on aggressive/antisocial behaviour

In addition to this rare mutation, functional variants of the *MAOA* that have less dramatic effect on enzyme activity exist and are common. By far the most studied of these is the VNTR polymorphism in the promoter region of the gene first described by Sabol et al., 1998. This polymorphism comprises 2–5 repeats whereas, based on in vitro findings, the alleles with 4 or 3.5 repeats would lead to higher and alleles with 2, 3 or 5 repeats to lower expression of the gene. Alleles classified to low activity *MAOA* genotypes (*MAOA*-L) are associated with lower brain volume in the limbic regions (Meyer-Lindenberg et al., 2006), and in subjects with *MAOA*-L the responses of prefrontal cortex and amygdala to angry and fearful faces were found to be diminished or increased, respectively. Differences in grey matter volume have also been reported for orbitofrontal cortex (Cerasa et al., 2008). *MAOA* genotype was also associated with inhibitory control and brain responses during relevant tasks (Passamonti et al., 2006). One study reported higher incidence of childhood abuse in subjects with the *MAOA*-L genotype that in males had been followed by higher impulsivity (Huang et al., 2004). In case of provocation the *MAOA*-L subjects express higher aggressiveness (McDermott et al., 2009) and indeed *MAOA*-L alleles are carried more frequently by violent and antisocially behaving males (Reif et al., 2007; Ficks and Waldman, 2014) including those with repeatedly expressed exceptionally violent behaviour (Tiihonen et al., 2015). *MAOA*-L males have not only been found more often to belong to an antisocial gang and to carry a weapon, but even among the gang members this genotype corresponded to higher probability of actual use of a weapon (Beaver et al., 2010).

Attempts have also been made to map the *MAOA* genotype into the larger framework of personality and underlying neurobiology. Given the many different ways to classify personality traits, it may not come as a surprise that no coherent picture has emerged. Instead, what may be revealing is that findings on aggressive and antisocial behaviour are much more consistent than any association with the broad personality factors. The broadly defined constructs include other facets that correlate with each other but appear to be biologically distinct; the broad constructs in different personality classifications again do share much with each other but contain variations that are probably not equivalent.

One study has compared a relatively small number of genotyped subjects preselected for extremes in peer-assessed neuroticism and found that highly neurotic subjects were more often carriers of the high functionality allele (Eley et al., 2003) but this was the case only in males. Another study did not find any association of the *MAOA* VNTR with Five-Factor Personality (that includes neuroticism) in postmenopausal women (Jurczak et al., 2015). Nevertheless, some findings from imaging studies may aid in further efforts to use MAO-A as a tool in the biology-based construction of theory of personality. Buckholtz and colleagues examined the relationship of *MAOA* genotype, Cloninger's tridimensional personality (Cloninger et al., 1993), and connectivity in the brain and found that *MAOA* L-allele carriers had lower activity in prefrontal cortical areas and increased connectivity between ventromedial prefrontal cortex and amygdala, whereas stronger coupling predicted higher harm avoidance (presumed to correspond to neuroticism) and lower reward dependence (Buckholtz et al., 2008). No direct effect of genotype on personality scores was reported, but a path analysis suggested that any genotype effect would be mediated via amygdala–vmPFC functional connectivity. In a study combining PET with genotyping (Alia-Klein et al., 2008), the Multidimensional Personality Questionnaire (that includes such constructs as harm avoidance, stress reactivity and negative emotionality) was used but no *MAOA* genotype effect was found. Nevertheless, findings on MAO-A activity (see 4.1) were supportive that the personality scale used could be informative on the role of MAO in shaping behaviour. Thus, *MAOA* genotype was not found associated with the MPQ trait aggression in this study, and other divergent findings have been reported on the simple association of *MAOA* genotype function and aggression. In one study high activity *MAOA* allele carriers were found not only to report higher level of aggressiveness and impulsivity, but also smaller prolactin response to fenfluramine was observed (Manuck et al., 2000), indicative of lower serotonergic capacity. Even this finding has been replicated (Beitchman et al., 2004; Kolla et al., 2014). One possible explanation of these apparently contradictory results is that they refer to the two distinct types of aggression: While the brain imaging studies would be consistent with the *MAOA*-L genotype being linked to the reactive type or defensive aggression, the MAOA-H genotype might be supporting callousness and proactive, predation-type aggression (Kolla et al., 2014). Using the competitive reaction time task, Kuepper et al. (2013) confirmed that the *MAOA*-L genotype is rather selectively associated with reactive, as opposed to proactive aggressiveness. Nevertheless, additional systematic research remains to be carried out to clarify the association of *MAOA* genotypes with potential subtypes of aggressiveness, and the state vs. trait aspects of these.

Because females have two alleles of *MAOA* one could wonder whether the number of low (or high) activity alleles matters. This issue has received very limited attention because of the possible silencing of one allele but it was reported (Sjöberg et al., 2007) that heterozygotes are placed between homozygotes in term of vulnerability to adverse psychosocial environment (see Section 5).

2.1.2. MAOA and substance use

MAOA genotype was not associated with alcohol dependence in a recent meta-analysis of eight studies (Forero et al., 2015). Another study that could not find a difference in allele distribution between alcoholic patients and controls however associated the *MAOA*-L genotype with higher impulsivity as measured with the Barratt Impulsivity Scale (Laqua et al., 2015). It could thus be so that researchers reporting significant genotype effect on alcohol abuse (e.g., Saito et al., 2002; Contini et al., 2006) have looked at a more specific type of patients. One study found that *MAOA*-L is associated rather with antisocial behaviour than with alcohol dependence itself (Samochoviec et al., 1999). Nicotine addiction has also been associated with the *MAOA*-L genotype (Jin et al., 2006). Dependence is obviously preceded by high level of consumption, and adolescent alcohol consumption has been found higher in *MAOA*-L males (Nilsson et al., 2011; but see Section 7).

2.1.3. MAOB, personality and monoamine metabolism

Despite the long tradition of studies on the association of the MAO-B isoenzyme activity on personality (see 4.2), attempts to identify a variation in the *MAOB* gene that would be functional or at least associated with behavioural measures have met only limited success. There are, however, reports of intron SNPs being associated with negative emotionality (Dlugos et al., 2009) of the Tellegen's Multiphasic Personality