Editorial

MAO and aggression

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This special issue, "Monoamine oxidase (MAO) and aggression", considers the evidence linking the monoaminergic neurotransmitters as regulated by the breakdown enzymes MAO A and B, and aggressive behavior. Encoded by separate genes on the X chromosome, MAO A and B both catalyze the breakdown of amines but have different catalytic properties and distinctly different distribution across the brain.

By way of introduction, Ramsay (2016) has reviewed the molecular aspects of MAO, focusing particularly on the B form of MAO (MAO B). MAO B is constitutively expressed throughout the body but is the predominant form in platelets and glial cells. Lower MAO activity means higher amine levels and vice versa as established by urinary and post-mortem measurements, or by microdialysis in rats. A brief description of the classic work on MAO expression is updated with recent observations of epigenetic regulation of MAO activity. MAO inhibition raises brain amine levels, a fact exploited for antidepressant effect, and now being incorporated into multi-target compounds to combat neurodegenerative conditions. Catalysis, mechanism and inhibition of MAO, important both for measuring levels in tissues and for drug design, are described. Of the successful irreversible drugs that inhibit MAO B, the classic non-selective MAO inhibitor, phenelzine, the MAO B-selective inhibitor deprenyl (selegiline, now commonly used in PD), and the cyclopropylamine, Parnate, are highlighted, along with labazemide as a reversible inhibitor. Recent developments in reversible inhibitor design include some compounds with nanomolar affinity but there is no indication that they will be successful *in vivo*. In the meantime, the traditional irreversible inhibitors are effective and well understood drugs.

Behavioral links with MAO activity have been greatly advanced by recent translational work informed by transgenic mice. In their article, Godar and colleagues (Godar *et al.*, 2016) review the role of monoamine oxidase A (MAOA) in the ontogeny of aggression. The first discovery of a connection between the *MAOA* gene and antisocial behavior came from the identification of a rare null-allele mutation and high propensity for violent crimes in the males of a Dutch family. Following this finding, several investigations have identified that aggression propensity is influenced by a functional VNTR (variable number of tandem repeats) polymorphism of the promoter of this gene; in particular, numerous independent studies have shown that low-activity VNTR alleles may interact with child abuse and/or neglect to facilitate the development of aggressive traits in adolescence and adulthood. In addition, several brain-imaging studies have identified that MAOA low-activity alleles are associated with alterations of cortico-amygdalar connectivity. The neurobiological underpinnings of these phenomena, however, remain poorly understood. A promising tool to investigate these issues is afforded by animal models, most notably mice harboring hypomorphic mutations of *Maoa*. Phenotypical analyses of these transgenic animals have revealed numerous elements of convergence with human data; in particular, Godar *et al.* show how the integration of animal and human studies is likely to refine our current understanding of the neurodevelopmental mechanisms of aggression, and assist in the development of novel therapies.

Harro and Oreland (2016) cover the history and state of the art of the studies describing the links between MAO and personality, with focus on alcohol abuse. Both MAO-A and MAO-B have been implicated in shaping personality and regulation of behavior, but their stories differ with regard to how either of the

isoenzymes came to the research limelight, what has most frequently been measured, what has been found and what their roles appear to be. While most of the studies are consistent in associating both MAO-A and MAO-B with impulsive, aggressive or antisocial personality traits or behavior, there are notable exceptions, and attempts to explain these divergent findings has provided insights into the salience of developmental aspects and gender roles. Adverse environmental factors, especially in childhood, strongly interact with the MAO measures in predicting future behavior but, importantly, the "risk variants" seem to increase not simply vulnerability but plasticity, hence being advantageous in supportive environments. Nevertheless, there is little evidence that variation in MAO activity in adulthood is the source of variation in the brain plasticity; indeed, it may be that the time window is already in the fetal period when monoamine neurotransmitters elicit their neurotrophic effects and serve as a source of differences in brain structure and functional connectivity. A possibility to look into this early period is provided by the only isoenzyme present in platelets (MAO-B) that remains uninfluenced by the epigenetic effects of life events on the brain and may inform on the enzyme activity during early development. While the location of the MAO genes on the X chromosome obviously contributes to at least some of the sex differences found in gene-environment interactions, the gender roles may act as hitherto unrecognized significant mediators that lead to the remarkably different findings in males and females (Harro and Oreland 2016).

The review by Fisar (2016) describes drugs use to inhibit monoamine oxidase activity, the role of monoamine neurotransmission in neuropsychiatric disorders with connection to MAO activity, and the therapeutic role of MAO inhibitors. The paper focuses on regulation of monoaminergic neurotransmission by the drug-induced

regulation of MAO, including recent developments showing that some drugs function both as inhibitors of MAO activity and as modulators of gene expression. The association between the disturbances in monoamine systems and MAO activity with the pathogenesis of depressive disorder, schizophrenia, bipolar disorder, drug addiction, pathological aggression and Parkinson's and Alzheimer's diseases is described. Finally, new hybrid drugs that inhibit MAO or other mitochondrial enzymes are introduced to cover the latest developments for the treatment of the latter degenerative disorders. (Fisar, 2016).

The Borovecki group review (Gotovac *et al.*, 2016) describes recent data on the biomarkers of aggression in dementia. This review focuses on the current literature regarding neuropsychiatric symptoms, especially agitation and aggressive behavior in dementia. Since the rate of aggression correlates with loss of independence, cognitive decline and poor outcome in patients with dementia, search for neurobiological, neurochemical, and genetic biomarkers of these behaviors might provide better understanding of their etiological background. The genetic markers described include genes encoding components of the serotonin system (for tryptophan hydroxylase, serotonin transporter and 5-HT2A receptor gene), apolipoprotein E (APOE), dopamine receptor, MAO-A and MAO-B, and genetic loci in the serine/threonine kinase 11 (STK11) and visinin-like 1 (VSNL1) genes. Neurotransmitter biomarkers associated with aggression in dementia are related to parts of the dopamine, norepinephrine, acetylcholine, glutamate, serotonin, and GABA systems. Neuropathological changes in aggression include increased atrophy in frontal and cingulated cortices, amygdala, hippocampus and insula. Some CST biomarkers such as increased levels of P-tau and T-tau were associated with apathy, while a negative

correlation was found between the levels of CSF Aβ1-42 and increased aggressive behavior. Management of aggression and agitation includes pharmacological (off label use of atypical antipsychotics; promising new drugs in the Phase II and III trials - brexpiprazole (dopamine D2 receptor partial agonist) and mibampator, dextromethorphan/quinidine, cannabinoids, and citalopram) and non-pharmacological (sensory, psychological and behavioral) treatments (Gotovac *et al.,* 2016).

In the only research article in this special issue, Pivac's group (Nikolac Perkovic *et al.,* 2016) presented their clinical data on MAO and agitation in psychiatric patients. The authors aimed to evaluate the possible association of either the activity or genetics of MAO (i.e platelet MAO-B activity, and two polymorphisms related to MAO-B and MAO-A genes: *MAOB* rs1799836 polymorphism and *MAOA*-uVNTR polymorphism) with severe agitation in psychiatric patients. Some hypotheses associate agitation and high aggression in psychiatric patients with reduced platelet MAO-B activity, and with the more frequent presence of the low (3-repeat; 3R) activity variants of the *MAOA* uVNTR polymorphism. This study included 363 subjects with schizophrenia and conduct disorder. Agitation was selected as a construct of pathological behavior **(**in line with Research Domain Criteria, RDoC**)** present in different psychiatric disorders. Severe agitation was significantly associated with smoking and with platelet MAO-B activity. Nikolac Perkovic *et al.* (2016) suggested that platelet MAO-B activity might be useful in differentiating subjects with or without severe agitation. On the other hand, in contrast to their hypothesis, severe agitation was not associated with *MAOA*-uVNTR or *MAOB* rs1799836 polymorphism, nor did these data show any association between the individual *MAOB* rs1799836 and *MAOA* uVNTR variants and severe agitation in subjects with

schizophrenia and conduct disorder. The authors concluded that agitation, which develops in many psychiatric disorders, has complicated etiology. Monoaminergic imbalance, together with deficits in other neurotransmitter systems, complicated with the interactions with different environmental and developmental factors, may contribute to the expression of agitation (Nikolac Perkovic *et al.*, 2016).

Literature

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