Progress in Neuro-Psychopharmacology & Biological Psychiatry 69 (2016) 131–146

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Monoamine oxidase and agitation in psychiatric patients

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ARTICLE INFO

Article history:
Received 30 November 2015
Received in revised form 15 January 2016
Accepted 2 February 2016
Available online 4 February 2016

Keywords:
Agitation
Platelet MAO-B activity
MAOB rs1799836 polymorphism
MAOA uVNTR polymorphism
Schizophrenia
Conduct disorder

ABSTRACT

Subjects with schizophrenia or conduct disorder display a lifelong pattern of antisocial, aggressive and violent behavior and agitation. Monoamine oxidase (MAO) is an enzyme involved in the degradation of various monoamine neurotransmitters and neuromodulators and therefore has a role in various psychiatric and neurodegenerative disorders and pathological behaviors. Platelet MAO-B activity has been associated with psychopathy- and aggression-related personality traits, while variants of the *MAOA* and *MAOB* genes have been associated with diverse clinical phenotypes, including aggressiveness, antisocial problems and violent delinquency. The aim of the study was to evaluate the association of platelet MAO-B activity, *MAOB* rs1799836 polymorphism and *MAOA* uVNTR polymorphism with severe agitation in 363 subjects with schizophrenia and conduct disorder. The results demonstrated significant association of severe agitation and smoking, but not diagnosis or age, with platelet MAO-B activity. Higher platelet MAO-B activity was found in subjects with severe agitation compared to non-agitated subjects. Platelet MAO-B activity was not associated with *MAOB* rs1799836 polymorphism. These results suggested the association between increased platelet MAO-B activity and severe agitation. No significant association was found between severe agitation and *MAOA* uVNTR or *MAOB* rs1799836 polymorphism, revealing that these individual polymorphisms in *MAO* genes are not related to severe agitation in subjects with schizophrenia and conduct disorder. As our study included 363 homogenous Caucasian male subjects, our data showing this negative genetic association will be a useful addition to future meta-analyses.

1. Introduction

Different psychiatric disorders, including schizophrenia and conduct disorder, have debilitating effects on patients and their families, causing them great suffering and carrying enormous mental health and societal burden as well as financial costs to the whole society. These complex and multifactorial mental disorders are rarely isolated, and commonly co-occur with other comorbid psychiatric disorders that complicate their clinical features as well as treatment. Patients with these disorders are frequently non-responsive or only modestly responsive to current treatment options. Therefore, the identification of the risk markers and biomarkers specific for these disorders may improve our understanding of the etiology/pathophysiology of these diseases, and provide novel drug targets. However, the putative biomarkers for various complex psychiatric diseases, such as schizophrenia and conduct disorder, are still missing (Chan et al., 2014). Although the understanding of biological pathways involved in the development of these disorders is improving, novel strategies focused to find reliable biomarkers and to improve treatment response are still rare. According to the Biomarkers Definitions Working Group, as part of the NIH Director's Initiative on Biomarkers and Surrogate Endpoints, a biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention or other health care intervention". Molecular biomarkers (Schmidt et al., 2013) can be assessed on different molecular levels, namely, on the genetic level (DNA biomarkers), the gene expression level (RNA biomarkers), the level of proteins (peptide and protein biomarkers), and epigenetic level, which regulates the gene expression by several mechanisms, namely, DNA methylation, histone modifications, and RNA interference (epigenetic biomarkers).

Blood cells represent a good, easily available and non-invasive biological material for biomarker screening (Mohr and Liew, 2007), as they share more than 80% of the transcriptome with other tissues

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http://dx.doi.org/10.1016/j.pnpbp.2016.02.002
0278-5846/

(brain, colon, heart, kidney, liver, lung, prostate, spleen and stomach). Deficits in human brain function can be assessed either "post-mortem" in the specific brain regions, or by the use of neuroimaging and nuclear magnetic resonance (NMR) spectroscopy. Other common approaches include genetics/genomics, transcriptomics, proteomics (Chan et al., 2014) and epigenetics (Shumay et al., 2012). At the metabolite level, evidence is provided (Chan et al., 2014) that molecular profiling analysis of blood serum/plasma can reveal robust molecular changes in psychiatric patients, suggesting that these changes are detectable besides in the brain, also in other body systems such as the circulating blood. Although peripheral biomarkers might offer easily accessible tests which could make a significant improvement in diagnosis, treatment, and patient care (Bahn and Chan, 2015), validated and reliable biomarkers of different psychiatric disorders are still not identified (Zolad and Diamond, 2013).

The studies investigating the molecular profiles of body fluids (i.e. saliva, plasma or serum) and blood cells are promising areas of research aiming to identify peripheral biomarkers for psychiatric disorders (Bahn and Chan, 2015). There is an unmet need to find reliable and validated biomarkers of neuropsychiatric disorders, especially from the accessible peripheral fluids (e.g. blood), in order to facilitate early diagnoses, detect particular personality traits, symptoms and behaviors, prevent psychopathological behaviors and to advance their treatment, but also to improve prognosis and disease outcome (Chan et al., 2014). In the research of the biological underpinnings and reliable biomarkers of the specific endophenotypes, pathological behaviors, and different personality traits in neuropsychiatric disorders, human platelets have been used as a non-invasive model (Asor and Ben-Shachar, 2012). Platelets and neurons share some similar processes and contain some identical components of the serotonergic system (Camacho and Dimsdale, 2000; Yubero-Lahoz et al., 2013). In addition, similar pathologies are found in platelets and neurons in many neuropsychiatric diseases (Asor and Ben-Shachar, 2012). Therefore, platelets have been used as an easily obtainable model for neurobiological research in humans. Due to the complexity of the neurobiological changes in neuropsychiatric disorders, not one biomarker, but a combination of multiple biomarkers is expected to be associated with the alterations observed in specific pathological behaviors in neuropsychiatry. The quest for biomarkers is especially important in forensic psychiatry for the prediction of violent and assaultive behaviors, since these markers could improve the accuracy of risk assessments (Gustavson et al., 2010).

1.1. Monoamine oxidase (MAO)

Monoamine oxidase (MAO; E.C. 1.4.3.4) is a flavin-adenine-dinucleotide (FAD)-containing enzyme which is involved in the degradation of various biogenic amines. MAO exists in two forms, MAO-A and MAO-B, responsible for the oxidative deamination of different monoamine neurotransmitters and neuromodulators (Bortolato and Shih, 2011; Oreland, 2004; Shih et al., 1999). Both MAO subtypes degrade serotonin, melatonin, dopamine, norepinephrine and epinephrine, and different amines (tyramine, tryptamine, 2-phenylethylamine, octopamine and 3-iodothyronamine). MAO-A and MAO-B differ in their substrate preferences, immunological properties, molecular weight and anatomical locations, and they are inhibited by different inhibitors. MAO-A deaminates primarily serotonin, norepinephrine and epinephrine, while MAO-B degrades β-phenylethylamine and benzylamine. Both isoenzymes degrade dopamine, tryptamine and tyramine. However, when one subtype is absent, the other isoenzyme can take its role (Bortolato and Shih, 2011).

Both forms of MAO are localized on the outer membrane of the mitochondria and widely distributed throughout the body. Within the central nervous system MAO-B is expressed at highest levels in serotonergic neurons, histaminergic neurons and in glial cells, and MAO-A is localized primarily in catecholaminergic (dopaminergic and noradrenergic) neurons (Luque et al., 1995; Saura et al., 1994; Westlund et al., 1988). In the peripheral tissues MAO-A is localized in fibroblasts and placenta (Egashira and Yamanaka, 1981), liver and gastro-intestinal tract, while MAO-B is found in the liver (Billett, 2004), blood platelets and lymphocytes (Bond and Cundall, 1977; Bortolato and Shih, 2011). MAO inhibitors are used as antidepressants, but due to their multiple drug- and food-interactions and side effects, they are prescribed less frequently (Fiedorowicz and Swartz, 2014). However, these drugs still have a place in the treatment of atypical, treatment-resistant depression or bipolar depression (Shulman et al., 2013). They include phenelzine, tranylcypromine and isocarboxazid, as well as newer, selective and reversible drugs, such as the MAO-A inhibitor, moclobemide, and MAO-B inhibitor, selegiline.

1.1.1. Platelet MAO-B activity

Platelet MAO-B activity has been proposed to represent a biomarker of different personality traits and psychiatric vulnerability, including sensation-seeking behavior, novelty-seeking personality, extraversion, poor impulse control and predisposition for taking different risky behaviors (Harro et al., 2004; Oreland, 2004; Oreland and Hallman, 1995). Platelet MAO-B activity, assumed to be a biological marker of psychopathology, was found to be associated with psychopathy- and aggression-related personality traits (Stalenheim, 2004). It is presumed that MAO-B function in platelets is heritable and its heritability has been estimated around 0.77 (Pedersen et al., 1993). Using the transmission probability model, the familial transmission of MAO activity was consistent with either recessive or additive, but not with dominant inheritance (Baron et al., 1985). Platelet MAO-B has similar biochemical and pharmacological characteristics as the brain MAO-B (Oreland, 2004), and both brain and platelet MAO-B are encoded by the *MAOB* gene (Chen et al., 1992). Various *MAOB* gene variants might influence the protein expression and the activity of platelet MAO-B (Bortolato and Shih, 2011). In addition, platelet MAO-B activity was shown to be significantly affected by sex, age, and smoking (Oreland, 2004), as well as with other environmental factors, implicating possible epigenetic mechanisms (Shumay et al., 2012).

Many studies have reported reduced platelet MAO-B activity in subjects with disinhibited behaviors such as novelty-seeking behavior, low levels of harm avoidance, high impulsiveness and high levels of sensation seeking (Oreland, 2004; Oreland et al., 1999; Ruchkin et al., 2005; Shih et al., 1999). It has been hypothesized that low MAO-B activity may represent a nonspecific marker indicating a predisposition to distress or psychopathology in general, rather than to specific behavior or specific disorders (Ruchkin et al., 2005). However, alterations in both directions (i.e. increased as well as decreased platelet MAO-B activity) have been proposed to represent biological vulnerability to different behaviors and traits (Paaver et al., 2006), as there is no simple or linear relationship between pathological behaviors, traits and monoaminergic functioning (Paaver et al., 2006; Schalling et al., 1987).

Various results suggest that mutations and polymorphisms in *MAOA* and *MAOB* genes might differentially affect the turnover rates of dopamine and serotonin. Higher plasma and urine levels of monoamines processed by MAOs (norepinephrine, epinephrine and serotonin), along with their metabolites, such as normetanephrine, have been associated with CT genotype of the *MAOA* rs1137070 polymorphism (Dorszewska et al., 2013). Moreover, a high activity *MAOA* uVNTR variant has been also associated with higher levels of monoamine metabolites, homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in lumbar cerebrospinal fluid (CSF) (Jonsson et al., 2000; Williams et al., 2003; Zalsman et al., 2005). It has been found that patients with "Brunner syndrome", resulting from the mutation in the *MAOA* gene, have low concentrations of HVA, 5-HIAA and vanillylmandelic acid, confirming reduced monoamine degradation (Brunner et al., 1993), due to MAO-A deficiency. In addition, the increased MAO-B protein expression, and consequently the increased platelet MAO-B activity were shown to be associated with *MAOB* rs1799836 A allele (Jakubauskiene et al., 2012). However, platelet MAO-B activity was not associated