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Jokinen Jussi

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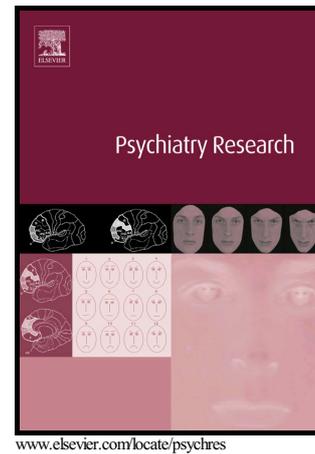
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Platelet monoamine oxidase activity and interpersonal violence in male suicide attempters

Jussi Jokinen^{a,b*}, Johan Königsson^b, Tomas Moberg^a, Erik G. Jönsson^{a,c}, Jari Tiihonen^{a,d}, Peter Nordström^a, Lars Orelund^e, Marie Åsberg^f

^a The Department of Clinical Neuroscience/ Center for Psychiatric Research, Karolinska Institutet

^b Department of Clinical Sciences, Umeå University, Umeå, Sweden

^c NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

^d Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland

^e Department of Clinical Sciences, Uppsala University, Uppsala, Sweden

^f Department of Clinical Sciences, Karolinska Institutet, Stockholm, Sweden

Abstract

Low platelet monoamine oxidase B (MAO-B) activity, proxy of low central serotonergic functions, has been shown to correlate with criminal behavior in adolescents that come from an unfavorable psychosocial environment but not in adolescents from good conditions, indicating a link between environment, MAO-B activity and aggressive behavior. The purpose of this study was to examine the association between MAO-B activity and lifetime interpersonal violence in suicide attempters. The study included a total of 28 suicide attempters (18 men and 10 women). Assessments of childhood exposure to and expressed interpersonal violence during childhood and as an adult were carried out with the Karolinska Interpersonal Violence Scale (KIVS). Platelet MAO-B activity was measured with 2-phenylethylamine (b-PEA) as substrate. Broken down by gender, the correlations between platelet MAO-B activity and both exposure scores to interpersonal violence as a child and expressed lifetime interpersonal violence were significant in male suicide attempters ($r = -0.61$, $p = 0.035$; $r = -0.84$, $p = 0.0005$), but not in women. Our finding of significant associations between interpersonal violence and low MAO-B activity need to be replicated in other cohorts of suicide attempters.

Address for correspondence:

Jussi Jokinen

Tel +46-73-6421446

E-Mail: jussi.jokinen@ki.se

Department of Clinical Neuroscience/Psychiatry

Karolinska Institutet

Karolinska University Hospital/Solna

SE-171 76 Stockholm, Sweden

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1. Introduction

Aggressive traits and impulsivity correlate with suicidal behavior, and the transmission of these behavioral endophenotypes mediate familial susceptibility for heightened suicide risk (Jokinen et al., 2010; McGirr et al., 2009; Rajalin et al., 2013). Early life adversity, like childhood physical or sexual abuse and/or neglect, is likely to lead to developmental dysregulation of behavioral and emotional traits mediating risk for suicidal and aggressive behaviors (Turecki et al., 2012). The balance in the serotonin system in the prefrontal structures and amygdala influences aggression and impulse control. Low serotonin activity facilitates increased aggression through reduced prefrontal inhibition (Rosell & Siever, 2015). Platelet monoamine oxidase B (MAO-B) activity can be considered as a proxy of central serotonergic functions and low platelet MAO-B activity has been associated with impulsive behaviors and suicidality (for review: Oreland et al., 2007; Harro & Oreland, 2016). MAO-B is, quantitatively, the dominating MAO in the human brain, and twin studies have shown that the thrombocyte enzyme activity is highly heritable; furthermore it is quite stable in the individual during lifetime. Interestingly, low platelet MAO-B activity has been shown to correlate with criminal behavior only in adolescents with early life adversity but not in adolescents from more favorable conditions, indicating a link between environment, MAO-B activity and aggressive behavior (Nilsson, 2006; Oreland et al., 2007; Harro & Oreland, 2016). The purpose of this study was to examine the association between platelet MAO-B activity and lifetime interpersonal violence in suicide attempters. Our primary hypothesis was that both high exposure to interpersonal violence as a child and more expressed violence would be associated with low platelet MAO-B activity. Since there are gender differences in serotonin-associated psychiatric conditions, such as depression and suicidal behavior, as well as violent behavior and platelet MAOB activity (Hawton, 2000; Weiss et al., 2006; Archer, 2004; de Almeida et al., 2015; Oreland et al., 2007), we also assessed men and women separately.

2. Methods

2.1 Study setting

Patients who were hospitalized after a suicide attempt at the psychiatric wards at the Karolinska University Hospital were proposed to participate in the study. The Regional

Ethical Review Board in Stockholm, Sweden, approved the study protocols (Dnr: 88–216; 91–96; 2010/3:4) and the participants gave their written informed consent to the study.

2.2 Participants

The study population involved 28 suicide attempters (18 men and 10 women) with a mean age of 43 years (S.D. = 13.6, range 23–66). Inclusion criteria were a recent suicide attempt and the age of 18 years or older. Exclusion criteria were schizophrenia spectrum psychosis, intravenous drug abuse, or if informed consent could not be obtained. Further, patients with diagnosed intellectual disability/mental retardation were not included. Suicide attempt was defined as any nonfatal, self-injurious behavior with at least some intent to die. Diagnoses according to DSM –III were established through the Structured Clinical Interview for DSM-III-, Axis I (SCID I) and Axis II (American Psychiatric Association). SCID II was not performed in four cases.

Ninety-three percent of the patients fulfilled criteria for at least one current Axis I or II psychiatric diagnosis. Fifty percent of the patients with Axis I diagnosis fulfilled criteria for a mood disorder, one third of the patients had an alcohol abuse diagnosis (either primary diagnosis or comorbid) and four patients had adjustment disorder as a primary Axis I diagnosis. Sixteen patients (57%) fulfilled criteria for a personality disorder, for type of personality disorder, please see the Supplement. Most of the patients were medication free at inclusion. In order to study biological risk factors in suicidal behavior, any psychiatric medication was discontinued and patients were medication-free with an average wash-out time of 8.6 days (SD 3.8, range 2–17). The study population has recently been described in detail; the patients were included between the years 1988–1991 (Jokinen et al., 2012).

2.3. *Thrombocyte monoamine oxidase activity*

Platelet MAO activity was measured with 2-phenylethylamine (β -PEA) as substrate, as described in Hallman et al. (1987). Briefly, samples of blood (5 ml) were drawn into Vacutainer tubes, and platelet-rich plasma was prepared by low-speed centrifugation. The platelet concentration was counted by a Coulter Counter (Dunstable, England) and the plasma frozen at -70 C until analysis. After thawing, the samples were sonicated four times 10 s each and estimation of the enzyme activity performed, by incubation at 37C for 4 min. with ^{14}C - β -phenylethylamine, final concentration 50 μM (New England Nuclear, Boston, Mass), as substrate. Substrate (β -PEA) resulted in linear relationship between amount of enzyme and

activity under these conditions. The estimations were carried out randomly and in duplicate and the mean values were used. Platelet MAO activity was measured in 23 suicide attempters.

2.4. Assessments

Patients were assessed with the Karolinska Interpersonal Violence Scale (KIVS) concerning early life adversity and expressed interpersonal violence. KIVS contains four subscales assessing exposure to violence and expressed violent behavior in childhood (between 6-14 years of age) and during adult life (15 years or older) (Jokinen et al., 2010). The KIVS scale is presented in supplementary file. The items are scored 0-5. The KIVS has previously been shown to have high inter-rater reliability as well as validity (Jokinen et al., 2010) and has been used in suicide research (Khemiri et al., 2016; Haglund et al., 2016). KIVS assessments were performed during the same period as blood sampling when patients were hospitalized after the suicide attempt. Exposure to interpersonal violence as a child and lifetime expressed violence were further analyzed in relation to MAO-B activity. Further, we did a post-hoc analysis of subscales expressed violence as a child and as an adult.

2.5. Data analysis

Initial analyses were carried out to evaluate skewness and kurtosis of the distributions with Shapiro Wilks test. The t-test and Kruskal-Wallis' test were subsequently used to investigate group differences (men and women) in continuous variables. Correlation analyses (Pearson's r) were used to determine associations between MAO-B activity and the three KIVS subscales. Fisher's z test was used to compare correlation coefficients (Pearson's r). The alpha was set at 0.05. The Statistical Package JMP 12.0.1 software, SAS Institute Inc., Cary, NC, USA was used for all statistical analyses.

3. Results

3.1 Clinical ratings of exposure to interpersonal violence as a child and expressed interpersonal violence as an adult

The mean exposure to interpersonal violence as a child was 2.5 (S.D. = 1.6, range 0-5) and the mean level of expressed interpersonal violence as a child and as an adult was 1.0 (S.D. = 1.2,

range 0-4) and 2.0 (S.D. = 1.2, range 0-5), respectively in suicide attempters. There were no significant differences in KIVS ratings between male and female suicide attempters (p values 0.16-0.4).

3.2. Platelet MAO-B activity (PEA) in suicide attempters

The mean platelet MAO-B activity in suicide attempters was 14.6 nmol of substrate oxidized per 10^{10} platelets per min, ($n = 23$, SD = 3.7, range 8.2–20.6, median 14.3). The mean platelet MAO activity did not significantly differ between male ($n = 13$, 14, SD = 3.9, range 8.2–19.9, median) and female suicide attempters ($n = 10$, 15.4, SD = 3.4, range 10.9–20.6, median 14.8) ($p = 0.38$). Platelet MAO-B activity did not correlate significantly with age ($r = -0.12$, $p = 0.57$). Platelet MAO-B activity was not associated with comorbid substance abuse diagnoses, depression severity or body mass index (p values of 0.35–0.72).

3.3. Platelet MAO-B activity and interpersonal violence in male and female suicide attempters

The correlations between platelet MAO-B activity and lifetime expressed interpersonal violence, as well expressed violence as a child and as an adult and exposure scores to interpersonal violence as a child were not significant in suicide attempters ($r = -0.37$, $p = 0.11$; $r = -0.26$, $p = 0.26$; $r = -0.34$, $p = 0.15$; $r = -0.36$, $p = 0.12$).

Broken down by gender, the correlation between platelet MAO-B activity and lifetime expressed interpersonal violence was significant in male suicide attempters ($r = -0.84$, $p = 0.0005$), Figure 1. The correlations between platelet MAO-B activity and both scores for exposure to interpersonal violence as a child and expressed interpersonal violence as an adult were significant in male suicide attempters ($r = -0.61$, $p = 0.035$ and $r = -0.75$, $p = 0.0053$, respectively), while platelet MAO-B activity showed a trend for significant correlation with expressed interpersonal violence as a child in male suicide attempters ($r = -0.55$, $p = 0.06$). Figure 2 shows the correlation between platelet MAO-B activity and exposure to interpersonal violence as a child in male suicide attempters.

The correlations between platelet MAO-B activity and the three KIVS subscales were non-significant in female suicide attempters ($r = 0.32$, $p = 0.44$; $r = 0.49$, $p = 0.22$; $r = -0.28$, $p = 0.51$). Supplementary Figure.

Comparisons of correlation coefficients indicate that there was a significant gender difference concerning correlation between MAO-B activity and lifetime expressed interpersonal violence (Fisher's $z = -3.40$, $p = 0.0007$) as well as expressed interpersonal violence as an adult (Fisher's $z = -2.71$, $p = 0.007$), but not with the two subscales measuring childhood interpersonal violence (Fisher's $z = 1.73$, NS; Fisher's $z = -0.76$, NS (all tests two-tailed)).

4. Discussion

In this study we found a negative correlation between MAO-B activity in platelets and expressed interpersonal violence as an adult in male suicide attempters. Male suicide attempters who reported more expressed interpersonal violence, like frequent fighting, repeated battering, physical or sexual abuse or convictions of crime of violence, had significantly lower MAO-B activity. The violent behavior was assessed with the Karolinska Interpersonal Violence Scale, which has been earlier shown to correlate to another marker of serotonin system: 5-hydroxyindoleacetic acid (5-HIAA), the serotonin metabolite measured in cerebrospinal fluid (CSF) in suicide attempters (Moberg et al., 2011). Our finding of significant associations between interpersonal violence and low platelet MAO-B activity, likely to be a proxy for low serotonergic neurotransmission, further validates behavioral dimensions measured with the Karolinska Interpersonal Violence Scale.

The finding of association between low platelet MAO-B activity and expressed violence in male suicide attempters is well in line with earlier research. Men with low platelet MAO activity run an increased risk of continued criminal behavior (Alm et al., 1994) and low platelet MAO activity has been associated with both different types of impulsive behavior (Guerrera, 1990) and suicidality (Buchsbaum et al., 1976; Buchsbaum et al., 1977; Meltzer&Arora, 1986). Further, low levels of platelet MAO activity have been reported in men with borderline personality disorder characterized by emotion dysregulation and anger dyscontrol, as well as in those with high levels of sensation seeking (Reist et al, 1990) and in men with type 2 alcoholism (Oreland, 2004).

Interestingly, in the present study low thrombocyte MAO-B activity was associated with higher levels of self-reported exposure to interpersonal violence as a child in male suicide attempters. Male suicide attempters reporting being bullied, punished corporally, beaten or sexually abused had lower MAO-B activity compared to those with low exposure to early life adversity. Platelet MAO-B activity in adulthood has been proposed to be a proxy marker for

monoaminergic activity during early development of the CNS (Oreland et al., 2007; Harro & Oreland, 2016). Early life adversity has an effect on the serotonin system, leading to dysregulation of inhibitory system of aggressive and impulsive behaviors, key endophenotypes in both suicidal and violent behaviors. Early life adversity is associated with persistent serotonergic abnormalities in animal models and in humans (Higley et al., 1992; Rinne et al., 2000). Rhesus monkeys exposed to maternal separation have persistently low levels of the serotonin metabolite 5-HIAA in CSF and show increased aggressive behaviour, loss of impulse control and increased alcohol intake (Higley&Linnoila, 1997). MAO-A and MAO-B are co-expressed in most human tissues. In the periphery, platelets and lymphocytes express only MAO-B. Low MAO-B activity can be seen as developmental response to hypofunctional serotonin system and MAO-B inhibition has proven in vivo influence over amine metabolism and behavior (Ramsay, 2016). Due to small sample size, we were unfortunately not able to assess the interaction effects of childhood exposure and violent behavior as adult used violence on platelet MAO-B activity.

Our results show a gender difference in the relation between MAO-B activity and expressed interpersonal violence as an adult; in female suicide attempters the correlations were not significant. This is in accordance with some earlier studies, which have reported gender differences in the MAOB activity in relation to behavioral measures (Oreland et al 2007). However, since the number of women in this study was low, the results need to be interpreted with caution. MAO-B expression is also modulated by glucocorticoids and by the sex steroids.

The strengths of this study include a well-characterized, medication-free patient cohort and well-standardized MAO-B activity measurements in platelets. There are also some limitations in this study, such as a small sample size. This abled us to detect only large effects and the gender specific approach had further effect on statistical power. Studies that are smaller might report effect sizes of larger magnitude, which may be the case in this study when comparing effect sizes in other studies of associations between MAO activity and comparable behavior measures. Further, negative results are often more questionable than positive results. Since we had a hypothesis driven approach, we did not adjust the results for multiple comparisons. Analyses of correlations between MAO-B activity and the two scales measuring expressed interpersonal violence as a child and as an adult in male suicide attempters can be seen as post hoc analyses. According to previous studies, smoking is a confounding factor in the association between different behaviors and MAO activity (Oreland et al., 2007). Unfortunately, this information was not systematically assessed which prevented us to assess whether smoking

behaviour mediates the effects of childhood adversity on MAO-B levels. One study has reported correlation between platelet MAO activity and sensation seeking, as measured using the Zuckerman Sensation Seeking Scale (SSS), among smoking and non-smoking male university students. Platelet MAO activity was negatively correlated with the Disinhibition and Total scales of the SSS both among smokers and non-smokers (Ward et al., 1987). In another study, smoking was a predictor of risk-taking traffic behavior, however, there was an association of platelet MAO activity with risk-taking traffic behavior while taking into account the smoking status (Luht et al., 2017).

Further, the sample may not be fully representative for a population of suicide attempters in general with more women attempting suicide. We did not have information concerning how many patients were eligible to participate during the study period, which is a limitation. However, the gender distribution of the sample can be seen as quite representative concerning serious suicide attempts needing inpatient care displaying a somewhat different gender distribution with more men.

In conclusion, we found in male suicide attempters significant associations between both expressed violence, exposure to interpersonal violence as a child and low MAO-B activity. Our finding of significant associations between lifetime interpersonal violence and low MAO-B activity need to be replicated in other cohorts of suicide attempters.

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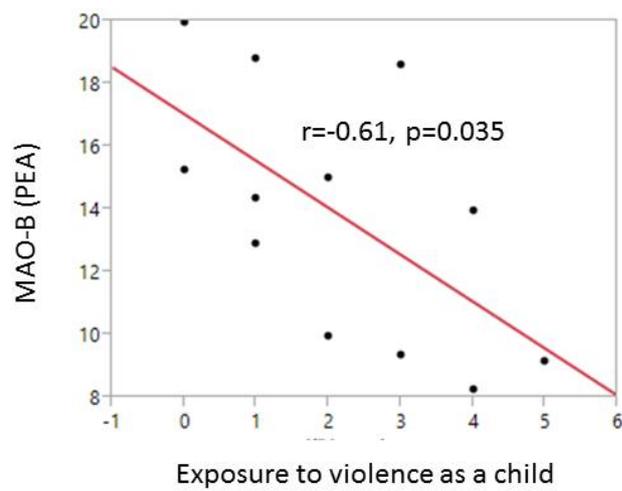
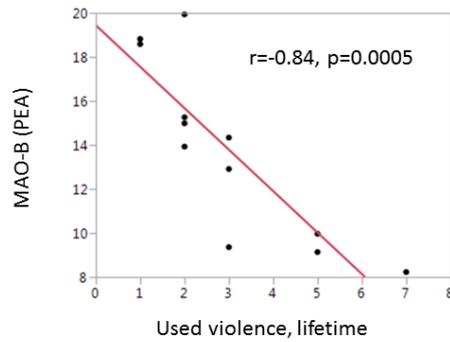
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Highlights:

- Platelet MAO-B activity showed a negative correlation with exposure to violence as a child.
- Platelet MAO-B activity showed a negative correlation with expressed violence.
- Correlations between MAO-B activity and KIVS were significant only in male suicide attempters.