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ORIGINAL ARTICLE

Salivary 5-hydroxyindole acetic acid (5-HIAA) in drug-naïve patients with short-illness-duration first episode major depressive disorder

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Abstract

OBJECTIVES: Central serotonergic dysfunction is reported in major depressive disorder (MDD). Serotonin is primarily metabolized to 5-hydroxyindole acetic acid (5-HIAA) and its plasma, urinary or cerebrospinal fluid concentrations were extensively studied in depression. No data is available on salivary 5-HIAA (s5-HIAA) in MDD to date.

METHODS: The basal, non-stimulated s5-HIAA concentration was studied in this cross-sectional case-control study on 20 non-late-life adult, short-illness-duration first-episode, treatment-naïve MDD patients and in 20 age- and sex-matched healthy controls. Depressed patients showed a score in the Hamilton Rating Scale for Depression (HAMD-17) higher than 20.

RESULTS: No significant difference in s5-HIAA concentration between patients with MDD and controls was observed. In post hoc analysis significantly lower s5-HIAA was seen in non-melancholic MDD (p=0.026) as related to controls whereas no difference was seen between melancholic MDD patients and controls. The concentration of s5-HIAA was not significantly correlated neither with duration nor the severity of depressive symptoms as measured by the total HAMD-17 score.

CONCLUSION: No difference was observed in baseline s5-HIAA concentration between MDD patients and healthy controls. That observation corroborates with previous MDD studies on 5-HIAA concentrations in bodily fluids where unaltered 5-HIAA concentration is seen in the absence of serotonin-related behaviours including impulsivity, suicidality, and anxiety. Salivary 5-HIAA use remains to be determined.

INTRODUCTION

Central monoaminergic dysfunction with low serotonergic activity is seen in major depressive disorder (MDD) (Malhi *et al.* 2005). Serotonin is principally metabolized via the action of monoamine oxidase, resulting in the formation of 5-hydroxyindole acetic acid (5-HIAA). The cerebrospinal fluid (CSF) 5-HIAA concentration has been adopted as an index of central serotonin turnover with plasma and urine 5-HIAA assessments being less extensively studied in MDD (Davis *et al.* 1988; Mitani *et al.* 2006). A lone study on tryptophan and its selected metabolites concentrations in saliva of healthy volunteers found measurable 5-HIAA concentrations (Riley *et al.* 1979).

Although some methodological discrepancies exist the 5-HIAA concentration is normal in the majority of MDD individuals while low 5-HIAA is rather associated with impaired impulse control, violent behaviour, suicide, heightened anxiety, exposure to psychotropics, and substance abuse being trait-like and independent of MDD (Davis *et al.* 1988; Placidi *et al.* 2001; Mann 2013; Bach *et al.* 2013). There is also some evidence for normal 5-HIAA levels in medication-free depressed patients that decreased following antidepressant fluoxetine treatment (De Bellis *et al.* 1993).

Our preliminary sampling showed measurable 5-HIAA concentrations within human saliva. So far, no report is available regarding salivary 5-HIAA (s5-HIAA) in MDD patients and healthy controls. Consequently, a case-control study was designed to determine saliva concentration of 5-HIAA, a serotonin metabolite, in a well defined cohort of first-episode, drug-naïve, short-illness-duration MDD patients and healthy subjects in baseline non-stimulated, stress-free conditions.

METHODS

Subjects

The study population has been described in detail elsewhere (Cubała & Landowski 2014). Briefly, 20, first-episode MDD patients were recruited and diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First *et al.* 1997). The depression severity was rated with 17-item Hamilton Rating Scale for Depression (HAMD-17) (Hamilton 1960). Subjects with HAMD-17 score of ≥20 with MDD being drug-naïve for any psychotropic medication and episode duration ≤24 weeks were eligible. Exclusion criteria were: any other Axis I disorder, psychotic symptoms, suicidality, somatic comorbidity, history of oral health problems including salivary gland disorders, concomitant medication including dietary supplements, hormonal contraception, pregnancy/lactation, BMI ≤18 and ≥30, age <18 and >55 years.

The control group consisted of 20 healthy subjects matched by age, sex, and metabolic parameters. They were interviewed with the Structured Clinical Interview for DSM-IV, nonpatient edition (First *et al.* 1997). A HAMD-17 score ≤5 was required for inclusion. None of them had a history of serious somatic disease or a family history of major psychiatric illness in their first-degree relatives. Exclusion criteria were: past exposure to psychotropic drugs, concomitant medication including dietary supplements, hormonal contraception, pregnancy/lactation, unstable medical condition, oral health problems including salivary gland disorders.

The study was carried out in accordance with the Declaration of Helsinki with the approval of the Ethic Research Committee of the Institution. For each study participant, written consent was obtained.

Study protocol

The study followed a cross-sectional, case-control design. All subjects fasted from midnight before the test day and arrived at the laboratory at 07:00 am. After the subjects had sat quietly for 45 minutes, saliva samples were taken for the assay of 5-HIAA at 08:20, 08:40, and 09:00 am using Salivettes (Sarstedt, Germany) placed in mouth and moved around in a circular pattern for 2 minutes. Collected samples were immediately stored at –80 °C with centrifugation after unfreezing for batch analysis. Sampling was performed between days 3 and 10 of the menstrual cycle in premenopausal women. The mean value from three samples was taken for analysis.

Assays

Salivary 5-HIAA concentrations were measured by an enzyme-linked immunoassay using an ELISA kit (ALPCO Diagnostics, USA). The inter- and intra-assay coefficients of variation (CV) were below 11.4% and 14.1%, respectively. The mean value from three samples was taken for analysis.

Statistical analysis

Statistical procedures were performed using StatsDirect v2.7.9. Shapiro-Wilk test was used to assess normal distribution of continuous data. Normally distributed variables were compared using Student's t-test, all other continuous data were compared with nonparametric Mann-Whitney U-test. The Spearman rank correlation coefficient was used to assess correlations between the obtained variables. All tests were two-tailed with an alpha=0.05.

RESULTS

Table 1 summarizes the demographic and clinical variables. There was no significant difference in s5-HIAA concentrations between depressed patients and controls. Post hoc analysis revealed significantly lower s5-HIAA in non-melancholic MDD (p=0.026) as related to controls. However, no significant difference was seen post hoc between melancholic MDD patients and controls. Both, depressive episode duration and severity were not correlated with s5-HIAA.

Tab. 1. Demographic and clinical variables.

		Control	MDD	MDD	
				melancholic	non-melancholic
N			20	9	11
Women (%)		60	55	55	54
Age (years)*	Median (IQR)	33.5 (30.3, 35.8)	30.5 (24.5, 37.5)	30** (25, 31)	31 (24, 44)
BMI	Mean (95% CI)	23.9 (22.6, 25.3)	22.8 (21.4, 24.1)	21.5*** (19.9, 23.2)	23.8 (21.6, 25.9)
WHR	Mean (95% CI)	0.82 (0.79, 0.86)	0.82 (0.73, 0.85)	0.82 (0.77, 0.87)	0.82 (0.77, 0.87)
Episode duration (weeks)	Mean (95% CI)	–	14.5 (12.2, 16.7)	14.9 (11.1, 18.7)	14.1 (10.9, 17.3)
HAMD-17*	Median (IQR)	1 (0, 2)	22.5 (21, 24)	24**** (23, 25)	21 (20, 22)
salivary 5-HIAA * (mg/L)	Median (IQR)	0.24 (0.15, 0.38)	0.16 (0.11, 0.29)	0.16 (0.16, 0.29)	0.11 # (0.03, 0.27)

* Shapiro-Wilk W p<0.05
** vs. Control: p=0.015, Mann-Whitney U-test, median difference (95%CI)= –5 (–10, –1)
*** vs Control: p=0.035, two-tailed, unpaired t-test, mean difference (95%CI)= –2.4 (–4.60, –0.17)
**** vs. Non-melancholic: p=0.002, Mann-Whitney U-test, median difference (95%CI)= 3 (2, 4)
# vs. Control: p=0.026, Mann-Whitney U-test, median difference (95%CI) = –0.13 (–0.24, –0.01)

There were no significant differences in terms of gender, age, BMI or WHR between patients with MDD and controls. Post hoc analysis revealed that melancholic MDD subjects were younger (p=0.015) and had lower BMI score (p=0.035) as related to controls. Post hoc analysis revealed the HAMD-17 score was significantly higher in patients with melancholia with regard to the subpopulation of non-melancholic MDD (p=0.002).

DISCUSSION

No significant difference in s5-HIAA concentration between MDD patients and controls was observed. The lack of an effect of depression on s5-HIAA is not particularly surprising. Central serotonergic function is altered in MDD. However, the evidence for MDD being caused by low levels of monoamines is inconsistent (Ruhé *et al.* 2007) and the concentration of 5-HIAA, the primary serotonin metabolite, in body fluids is hardly indicative of the central serotonin turnover (Mitani *et al.* 2006). The results are in line with studies reporting the 5-HIAA in body fluids being typically normal in non-suicidal depressed patients and low in individuals predisposed to violent suicidal behaviour and to violence-impulsivity. Low 5-HIAA was associated with impaired impulse control, violent behaviour, suicide, heightened anxiety, exposure to antidepressants, and substance abuse being trait-like (Davis *et al.* 1988; De Bellis *et al.* 1993; Placidi *et al.* 2001; Mann 2013; Bach *et al.* 2013). As this study results apply to drug-naïve patients with short-illness-duration first episode MDD who were free of comorbid Axis I and II conditions and suicide history it corroborates with data on unaltered 5-HIAA levels in non-suicidal depressed individuals and healthy controls. Thus, low 5-HIAA may not be confined to depression per se as it seems to be an independent trait marker correlating with variety of conditions including MDD with high impulsivity (Reimold *et al.* 2008; Bach *et al.* 2013; Mann 2013).

Significantly lower s5-HIAA in non-melancholic MDD as related to controls was found post hoc and no difference was observed between melancholic MDD individuals and controls. That observation may support hypothesized neurobiological differences between melancholic and non-melancholic depression. Serotonergic dysregulation is associated with all depressive subgroups. However, non-melancholic depression seems to be particularly serotonin dependent (Malhi *et al.* 2005). Low s5-HIAA found post hoc in non-melancholic MDD may be indicative of low serotonergic activity playing role in its pathophysiology (Reimold *et al.* 2008; Fitzgerald *et al.* 2009).

So far, 5-HIAA has been measured in brain tissue, CSF, plasma, and urine of MDD patients (Davis *et al.* 1988; Mitani *et al.* 2006). Our pilot experiment showed measurable 5-HIAA salivary concentrations providing methodology for this study. Salivary serotonin levels have been studied in headaches (Marukawa *et al.* 1996) and depression (Tan *et al.* 1997), where lower serotonin concentration was seen in depressed subjects as compared to healthy controls becoming normalised after

fluoxetine treatment. No data is available with regard to s5-HIAA in MDD to date and its functional importance is not clear. However, s5-HIAA assays may offer a promising, stress-free alternative to CSF 5-HIAA analyses that remain to be determined in future studies.

CONCLUSIONS

No difference was found in baseline s5-HIAA concentration between drug-naïve patients with short-illness-duration first episode MDD and healthy controls. The results corroborate with previous MDD studies on 5-HIAA concentrations in body fluids where unaltered 5-HIAA levels were seen in the absence of serotonin-related behaviours including impulsivity, suicidality, substance use, and anxiety.

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