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No major influence of regular tobacco smoking on cerebrospinal fluid monoamine metabolite concentrations in patients with psychotic disorder and healthy individuals☆

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ABSTRACT

Metabolism of the monoamines dopamine, serotonin and noradrenaline, is altered in the central nervous system of people with schizophrenia, and their major metabolites homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG), respectively, have been intensively studied as indirect measures of these neurotransmitters in cerebrospinal fluid (CSF). Regular tobacco smoking has been shown to alter neurotransmitter metabolism in the brain and studies have found CSF monoamine metabolite concentrations to be substantially lower in smokers. However, few studies investigating these monoamines in CSF have controlled for regular tobacco smoking. We investigated if regular tobacco smoking influences CSF HVA, 5-HIAA and MHPG concentrations in patients treated for psychotic disorders (n = 69) and healthy non-psychotic human volunteers (n = 200). After lumbar puncture CSF samples were analyzed with mass fragmentography. CSF HVA, 5-HIAA and MHPG concentrations did not significantly differ between smokers and non-smokers neither in patients, nor in healthy subjects, whereas back-length predicted HVA and 5-HIAA and antipsychotic medication MHPG concentrations. The results indicate that regular tobacco smoking has no significant effect on monoamine metabolite concentrations in CSF. This suggests that lack of controlling for regular tobacco smoking should not substantially violate the results in studies of the major monoamine metabolites in CSF.

1. Introduction

Researches regarding the pathophysiology of schizophrenia have to a substantial extent focused on dysfunction of neurotransmission in the central nervous system (CNS) (Owen et al., 2016). People with schizophrenia show increased synthesis capacity, release and baseline synaptic concentrations of dopamine (Howes and Murray, 2014). Increased dopamine synthesis capacity seems to be present already in the prodromal phase and is correlated with severity of symptoms in people with schizophrenia (Howes et al., 2012). Also serotonergic dysfunction plays a role in the pathophysiology of schizophrenia. Altered serotonin receptor availability has been implicated in mood and anxiety disorders that resemble the negative symptoms of schizophrenia (Selvaraj et al., 2014). Also, there is some evidence that serotonin transporter reuptake inhibitors can treat negative symptoms of schizophrenia (Sommer et al., 2012). Recreational drugs that are structurally similar to and bind to the same receptors as serotonin distort perception and induce paranoia much like what is seen in patients with schizophrenia (Selvaraj et al., 2014). A number of studies have found concentrations of noradrenaline to be altered in serum and plasma in people with schizophrenia and to correlate with the severity of symptoms in these patients. Some studies have also shown that substances affecting noradrenaline signaling, such as clonidine, can have a therapeutic effect on symptoms of schizophrenia (Bjerkenstedt et al., 1985; Fitzgerald, 2014). The major metabolites of dopamine, serotonin and noradrenaline are homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG), respectively.

Metabolites of relevant neurotransmitters have been investigated in both plasma and cerebrospinal fluid (CSF). CSF analysis is however thought to be the most reliable way to estimate cerebral metabolism

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due to the close proximity between CSF and the CNS, the high turnover rate of CSF and a molecular complexity that is more manageable than that of serum or plasma (Schwarz and Bahn, 2008). Several studies have shown a correlation between CSF monoamine metabolite concentrations and schizophrenia. For example CSF HVA has been shown to be lower in patients with psychotic morbidity compared to healthy controls, whereas CSF MHPG has been reported to be higher in patients (Bjerkenstedt et al., 1985; Hsiao et al., 1993; Lindström, 1985; Wieselgren and Lindström, 1998). CSF monoamine metabolites have also been implied as intermediate phenotypes between glutamate- and dopamine-related genes and schizophrenia (Andreou et al., 2014, 2015, 2016).

There are several important covariates that might influence monoamine metabolite concentrations in CSF. For example, height and back-length of the subjects have been shown to influence HVA and 5-HIAA concentrations, age has been associated with CSF 5-HIAA and gender has been shown to affect the MHPG concentration (Andreou et al., 2012; Malone et al., 2003).

Studies have shown both that people with psychiatric conditions are more likely to smoke and that smokers are more likely to have a psychiatric diagnosis. Among patients with schizophrenia, the smoking prevalence has been estimated to 65–90% and there is evidence that this over-representation might to some extent be explained by shared genetics for schizophrenia and smoking dependence (Aubin et al., 2012). Nicotine interacts with neurotransmitter systems, notably the dopaminergic mesolimbic system, and prolonged nicotine use has been shown to up-regulate nicotinergic acetylcholine receptors in the mesolimbic system (Aubin et al., 2012).

Considering this, a correlation between regular tobacco use and monoamine metabolites in CSF may be anticipated. Few studies have investigated this connection to date. One study investigating men with post-traumatic stress disorder (PTSD) and healthy controls, found that smokers had about half of the concentrations of CSF HVA compared to non-smokers (Geracioti Jr et al., 1999). Another study found a negative correlation between cigarette smoking and 5-HIAA in CSF among depressed patients with suicidal behavior (Malone et al., 2003). Other researchers found the correlation between plasma 5-HIAA and CSF 5-HIAA to be diminished in smokers compared to non-smokers but did not find any difference in CSF 5-HIAA concentrations between smokers and non-smokers (Strawn et al., 2002). In a study investigating depressed patients a US research team reported lower CSF MHPG concentrations among smokers than non-smokers (Galfalvy et al., 2009).

Notably, several studies that have investigated the relationship between schizophrenia and CSF monoamine metabolite concentrations have failed to control for regular tobacco smoking (Andreou et al., 2015; Bjerkenstedt et al., 1985; Lindström, 1985; Wieselgren and Lindström, 1998). Thus, there is need for additional studies investigating these associations. In a replication attempt of previous studies claiming lower monoamine metabolite levels in smokers (Galfalvy et al., 2009; Geracioti Jr et al., 1999; Malone et al., 2003), we investigated if regular tobacco smoking influences CSF HVA, 5-HIAA and MHPG concentrations in patients treated for psychotic disorders and healthy non-psychotic human volunteers.

2. Methods

2.1. Study population

The present study was approved by the Stockholm Regional Ethics Committee (2016/2305–32). Informed consent was obtained from all the participating subjects. Subjects were included between 1973 and 1989 in studies analyzing different aspects of CSF monoamine metabolite concentrations among patients with schizophrenia or related psychosis and non-psychotic controls subjects as previously described (Andreou et al., 2015; Jönsson et al., 1996). Included in the present study were 269 subjects, 170 men and 99 women for whom data on tobacco smoking (cigarettes/day) were available from a questionnaire filled in at the time when CSF was drawn ($n = 248$) or could be derived from data obtained at later re-investigations ($n = 21$). Out of these subjects, 200 (126 men, 74 women) were healthy controls recruited among students, hospital staff or from population registers. The other 69 (44 men, 25 women) had a diagnosis of schizophrenia spectrum disorder and were recruited during admittance to one of four hospitals in the Stockholm area. Inclusion criteria were that smoking status and monoamine metabolite concentrations had been recorded. For the subjects where data on back-length, defined as the distance between the external occipital protuberance and the point of needle insertion, were not available ($n = 64$), back-length was calculated from the relationship ($r = 0.66$) between height and back-length (Jönsson et al., 1996). For the subjects where data on height or weight were missing ($n = 29$ and $n = 12$ respectively), gender mean was used. Patients were excluded if no data was available on pharmacological treatment at the time of LP.

Fifty-four of the patients had a history of or were taking antipsychotic medication at the time of LP. Those who had not received any oral or intramuscular non-depot formulations of antipsychotic medication in the last 14 days or any depot formulations for the last three months were considered medication-free ($n = 29$). All healthy controls were medication-free with the exception of some of the female participants who were taking oral contraceptives (Jönsson et al., 1996).

2.2. Lumbar puncture

Lumbar punctures (LPs) were performed between 8 AM and 9 AM with the patient in a sitting or recumbent position. Prior to LP, all study participants had had at least eight hours of bed rest and abstinence from food, tobacco and drug treatment. During the LP, 12.5 ml of CSF was collected from each participant and was immediately centrifuged and stored at −20 °C. The CSF HVA, 5-HIAA and MHPG concentrations were determined by mass fragmentography within two months from sampling (Swahn et al., 1976).

2.3. Statistics

Independent *t*-tests and Mann-Whitney *U* tests (for continuous normally and non-normally distributed variables, respectively) and chi2 tests (for dichotomous variables) were used to investigate whether the study populations differed significantly regarding confounders such as back-length, height, weight, gender, age and antipsychotic treatment. According to Shapiro-Wilk's test age, height, weight, HVA, 5-HIAA and MHPG were not normally distributed.

The effect of regular tobacco smoking on CSF HVA, 5-HIAA and MHPG concentrations was evaluated using Mann-Whitney *U* tests. To further verify the results we also performed multiple regression analyses taking potential confounders into account. Residuals of the multiple linear regressions were normally distributed. Using multiple linear regressions, the concentration of each monoamine metabolite was modeled as a function of smoking status (smoking/no smoking) and the following covariates: height, back-length, weight, gender, age and antipsychotic treatment. To evaluate if the results were violated using estimates of back-length, multiple regressions were also performed including only those subjects with back-length data measured at LP.

Statistical power was computed using G*Power ver. 3 freeware Power calculator (Erdfelder et al., 1996). The software used for the statistical analyses was IBM SPSS ver. 23. The threshold for significance was set at $p < 0.05$.

3. Results

3.1. Descriptive statistics

A total of 269 subjects were included in the study. Out of these, 129