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A tetrahydrobiopterin deficit finding in schizophrenia: A confirmation study

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Keywords

Schizophrenia; Tetrahydrobiopterin deficit; GTP cyclohydrolase I gene variant

Dear Editor:

Tetrahydrobiopterin (BH_4) is a vital cofactor that maintains availability of amine neurotransmitters such as dopamine and serotonin, regulates nitric oxide synthesis, and stimulates and modulates the glutamatergic system (Thony et al., 2000; Sumi-Ichinose et al., 2001). Dysregulation of these neurotransmitter systems has been implicated in the pathogenesis of schizophrenia (reviewed in Morrison and Murray, 2018). BH_4, the oxidized quinonoid dihydrobiopterin (BH_2), and biopterin constitute total biopterins in circulating blood (Thony et al., 2000). We and others have reported significantly lower fasting plasma or serum total biopterins in patients with schizophrenia (Richardson et al., 2005; Teraishi et al., 2018) and schizoaffective disorder (Richardson et al., 2007), which has been considered to likely reflect a physiologically significant BH_4 deficit due to reduced levels of CNS amine neurotransmitters (reviewed in Richardson et al., 2007). It has been hypothesized that

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Contributors

Concept and design: Dr. James D. Clelland (JDC) and Dr. Catherine L. Clelland (CLC). Acquisition of human samples and data: JDC, Dr. Jennifer Smeed, Dr. Serge Cremers, and CLC. Statistical analysis and interpretation of results: JDC and CLC. Writing of the manuscript: JDC and CLC. All authors contributed to and have approved the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.06.006.

Declaration of Competing Interest

Dr. Catherine L. Clelland (CLC) and Dr. James D. Clelland (JDC) are inventors on a patent that is based in part upon this study data. CLC and JDC may benefit financially in the future if the patent is licensed. CLC and JDC declare no other financial relationships that are directly or indirectly related to this work. The remaining authors (Dr. Smeed and Dr. Cremers) declare no conflict of interest.

alleviation of this deficit may prove to be a beneficial treatment approach for patients (Okusaga, 2014) and thus the aim of this current study was to confirm the presence of a BH_4 deficit in schizophrenia patients.

In a new sample of 90 patients with DSM IV schizophrenia and 65 control subjects (see Supplementary methods and results), well-matched by gender, race/ethnicity and age, we assayed fasting plasma BH_4 levels via the method of (Fekkes and Voskuilen-Kooijman, 2007, see also Supplementary methods). The *GCH1* gene encodes the first and rate-limiting enzyme in BH_4 biosynthesis, and significantly lower peripheral *GCH1* expression has been reported in patients with first-episode psychosis (Ota et al., 2014). The rs10137071 *GCH1* promotor variant (G to A allele) has also been associated with reduced gene expression and a deficit of total biopterins in patients with schizophrenia and schizoaffective disorder (Clelland et al., 2018). Thus, subjects were also genotyped for the rs10137071 promotor variant.

In our primary analysis, simple linear regression was employed to model the relationship between diagnostic group (patients versus controls) and ln (BH_4). Based upon our previous studies of total biopterins (Richardson et al., 2005; Richardson et al., 2007) and *GCH1* expression (Clelland et al., 2018), the covariates of fasting phenylalanine level, ethnicity, age, and medications found to predict peripheral expression in patients (risperidone, valproate and olanzapine), were tested in a full multivariable model and sequentially a nested model which carried forward only terms with p-values <0.05. Model fit was determined using the Likelihood ratio test and confirmed via Akaike information criterion (AIC) and Bayesian information criterion (BIC).

In both the full and nested models we observed a significant effect of diagnostic group on fasting BH_4 levels ($p<0.05$). Retaining the covariate of risperidone use in the final model (LR test χ^2 (6)=3.75, p=0.71; AIC/BIC nested model < full model), the results indicated that schizophrenia patients had ln (BH_4) levels on average 22% lower than control subjects (Fig. 1, n=155, $p<0.05$). A stratified analysis, excluding all patients receiving risperidone, replicated the model finding. Analysis of total biopterins as the dependent variable in an analogous full model also revealed as anticipated, lower fasting plasma levels in the schizophrenia patients as compared to the control group, however the effect did not reach two-tailed significance (n=155, $\beta=-2.686$, $t_{0146}=-1.81$, 1-tailed p=0.036), possibly due to the smaller numbers investigated here than in previous studies of total biopterins (Richardson et al., 2005; Teraishi et al., 2018).

We previously observed a significant linear relationship between total biopterins and *GCH1* genotype in patients (Clelland et al., 2018), and thus in a secondary analysis (due to multicollinearity of predictor variables), we investigated the relationship between fasting plasma ln (BH_4) and the three level ordinal genotype by diagnostic group: controls (n=65), GG patients (n=26), A allele patients (n=64). There was a significant linear relationship ($\beta=-0.194$, $t_{152}=-2.05$, p=0.042), and interpretation of the β coefficient indicates that there is on average a 19% lower ln (BH_4) between each level, following adjustment for risperidone use; schizophrenia patients with the variant A allele (AA and GA genotypes) having BH_4

levels lower than GG patients, who had ln (BH_4) lower than controls (Supplementary Fig. S1).

In summary, previous studies of circulating total biopterins have pointed to the presence of lower fasting BH_4 levels in schizophrenia patients. We now show a significant BH_4 deficit in a new sample of patients compared to a matched control subject group. The results of this study provide further support for research into therapeutics for alleviating the BH_4 deficit, which may be particularly beneficial in patients carrying the variant allele.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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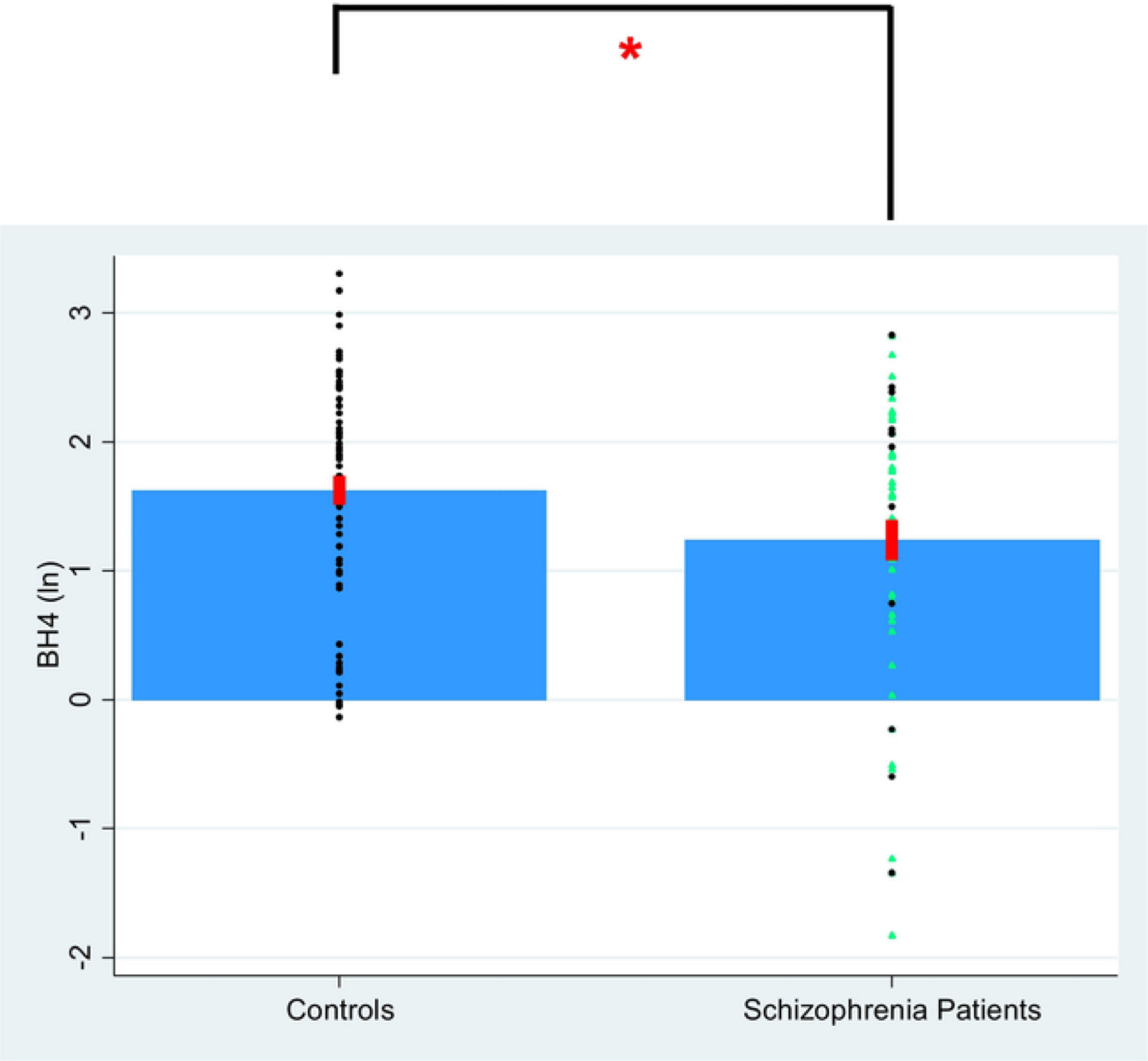

Fig. 1.

BH_4 levels are significantly lower in patients with schizophrenia. In the fitted model ($F_{2,152}$ =3.16, p=0.045) there was a significant effect of diagnostic group on fasting plasma ln (BH_4) (β=−0.38, t_{152} =−2.15, *p=0.033), following adjustment for risperidone use (yes, no). Schizophrenia patients (n=90, adjusted mean =1.34, standard error=0.11) had on average BH_4 levels 22% lower than controls (n=65, adjusted mean =1.73, standard error=0.13). Following a stratified analysis which excluded patients receiving risperidone (n=36), the significant effect of diagnostic group remained (β=−0.38, t_{117} =−2.03, p=0.045). Means (ln) are plotted for each diagnostic group, with SEM's represented by the internal box (red) within each bar. Individual subject points are depicted by black jittered dots for controls and GG patients, and green triangles for A allele patients (AA and GA genotypes). Statistical

analyses were conducted using STATA v14.2 (College Station, TX). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)