Reversal of imbalance between kynurenic acid and 3-hydroxykynurenine by antipsychotics in medication-naïve and medication-free schizophrenic patients


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ABSTRACT

The association between the pro-inflammatory state of schizophrenia and increased tryptophan degradation into kynurenine has been reported. However, the relationship between metabolites from subdivisions of the kynurenine pathway, kynurenic acid and 3-hydroxykynurenine, remains unknown. The present study tested the relationship between these kynurenine metabolites in the plasma of medication-naïve (n = 35) or medication-free (n = 18) patients with schizophrenia at admission and following 6-week antipsychotic treatment compared to healthy controls (n = 48). The plasma concentrations of kynurenic acid (nmol/l) were lower (difference = −8.44 (−13.22 to −3.65); p = 0.001) and of 3-hydroxykynurenine (nmol/l) were higher (difference = 11.24 (8.11–14.37); p < 0.001) in the patients compared with the healthy controls. The kynurenic acid/kynurenine (difference = −2.75 (−5.115 to −0.336); p = 0.026) and kynurenic acid/3-hydroxykynurenine (difference = −1.08 (−1.431 to −0.729); p < 0.001) ratios were also lower in the patients. After the 6-week treatment, the patients’ plasma kynurenic acid levels (difference = 3.85 (−0.23 to 7.94); p = 0.064) showed a trend towards an increase, whereas plasma 3-hydroxykynurenine levels (difference = 22.41 (19.76–25.07); p < 0.001) decreased. As a consequence, the kynurenic acid/3-hydroxykynurenine ratio (difference = −4.41 (−5.51 to −3.3); p < 0.001) increased. Higher initial plasma kynurenic acid levels on admission or increased kynurenic acid/kynurenine ratio after treatment were associated with reduction of clinical symptoms scores upon discharge although higher kynurenic acid/kynurenine on admission may induce higher positive symptoms score. In contrast, higher 3-hydroxykynurenine is associated with lower positive symptoms score. These results indicate that there is an imbalance in the kynurenine pathway in schizophrenia. The 6-week antipsychotic treatment may partially reverse the imbalance in kynurenine metabolism and that in turn induces clinical response.

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