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Letter to the Editor

Serum xanthurenic acid levels: Reduced in subjects at ultra high risk for psychosis

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Dear Editor,

The kynurenine pathway of L-tryptophan metabolism generates neuroactive compounds that interact with central nervous system glutamate receptors implicated in the pathophysiology of schizophrenia (Schwarcz et al., 2012). In particular, the kynurenine metabolites, kynurenic and quinolinic acids, respectively inhibit and activate *N*-methyl-D-aspartate (NMDA) glutamate receptors, and may alter activation of NMDA in schizophrenia (Moghaddam and Javitt, 2012).

Recently, xanthurenic acid (XA), a kynurenine pathway metabolite produced by transamination of 3-hydroxykynurenines, was found to activate mGlu2 metabotropic glutamate receptors (Fazio et al., 2017, 2018). These receptors are drug target-candidates for schizophrenia because their activation inhibits 5-HA_{2A} receptors (Marek et al., 2000) and limits glutamate release in prefrontal cortex (Moghaddam and Adams, 1998). Accordingly, systemically administered XA displayed antipsychotic-like behavioral effects in mice challenged with the NMDA-receptor antagonist MK-801 (Fazio et al., 2015). Serum concentrations of XA were significantly *lower* in patients with schizophrenia than in healthy controls, regardless of the clinical status of the disorder or its treatment, as well as in their first-degree relatives (Fazio et al., 2015). These findings support the hypothesis that reduced activation of mGlu2 receptors may contribute to the pathophysiology of schizophrenia.

Growing evidence suggests that glutamatergic dysfunction may occur in prodromal phases of schizophrenia and that is not affected by treatment with available antipsychotics (Moghaddam, 2013). These findings led us to assay serum concentrations of XA and other kynurenine metabolites in subjects at ultra-high risk (UHR) for psychotic illness versus healthy controls.

1. Methods

This study was approved by the relevant Ethical Committee, and subjects provided written, informed consent. Exclusion criteria were: (i) the presence of major psychiatric or medical disorders, or cognitive disability; (ii) lifetime history of any Axis I psychiatric disorder; and (iii) use of abused substances within the preceding three months. We rated the Ultra High Risk for Psychosis syndrome with the Structured Interview for Prodromal Syndromes (SIPS) and Scale of Prodromal Symptoms (SOPS) and all UHR subjects met criteria for Attenuated Psychosis Syndrome (APS) (Miller et al., 1999). We compared 10 UHR subjects with 25 age-matched healthy volunteers. After 12 months from intake, psychiatrists responsible for UHR subjects ascertained whether subjects became overtly psychotic and met DSM-5 criteria for schizophrenia.

We assayed serum concentrations of XA, L-tryptophan, L-kynurenine, kynurenic acid, anthranilic acid, quinolinic acid, 3-hydroxykynurenine, and 5-hydroxyindoleacetic acid, using a validated liquid chromatography/tandem mass spectrometry method (Fazio et al., 2015). Data analyses (Mann-Whitney [*U*] or contingency table [χ^2] tests compared subject-groups) used commercial SPSS.21 software (IBM-SPSS Inc., Chicago, IL).

2. Results

UHR patients and healthy controls did not differ significantly in age, sex-distribution, BMI, or lifetime substance abuse (Table 1). UHR cases had 30.4% higher serum concentrations of L-tryptophan than controls, whereas XA levels were 39.3% lower, and individually computed [tryptophan]/[XA] concentration ratios averaged 2.24-times higher in UHR subjects than in controls (Table 1). After 12 months, 4/10 UHR subjects met diagnostic criteria for schizophrenia, and their XA levels did not differ significantly from those who did not become overtly psychotic (not shown).

3. Conclusions

We had found previously that serum XA concentrations were reduced in a large cohort of subjects with schizophrenia and their first-degree relatives, and were not altered by a year of treatment with second-generation antipsychotics (Fazio et al., 2015). The present findings extend analysis of XA and other kynurenine metabolites to subjects at high risk to become overtly psychotic, but did not meet DSM-5 criteria for schizophrenia. Although the present subject-count is moderate, the new findings suggest less efficient metabolic conversion of L-tryptophan to XA through the kynurenine pathway in UHR subjects. These changes were quite selective as circulating levels of other kynurenine metabolites were unchanged.

These findings add support to the hypothesis that activation of mGlu2 receptors is reduced in prodromal as well as in clinically overt schizophrenia. If activation of mGlu2 receptors is deficient in schizophrenia and its prodromes, treatments targeting these receptors might be worthy of exploration (Kinon et al., 2015). In conclusion, serum concentration of XA may represent a useful biomarker that can facilitate identification of UHR individuals who might benefit from mGlu2-targeting treatments in prodromal or early phases of schizophrenia.

Conflict of interests

All the authors and immediate family members have no financial involvement with any organization that might appear to represent a potential conflict of interest with the information in this manuscript.

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Table 1
Serum concentrations of kynurenine metabolites and other factors in subjects at ultra-high risk (UHR) for psychosis compared to healthy controls.

Measures	Healthy controls	UHR cases
Subjects (n)	25	10
Sex (% females)	30.0	55.6
Age (years)	21.6 ± 3.80	23.3 ± 1.63
Body-mass index	21.5 ± 1.73	22.0 ± 1.86
Drug abuse (%)	3.70	10.0
Alcohol use (%)	3.70	0.00
Smoking (%)	29.6	10.0
L-Tryptophan (μg/mL)	4.40 ± 1.17	5.74 ± 1.33*
Kynurenine (μg/mL)	0.35 ± 0.12	0.55 ± 0.59
Kynurenic acid (ng/mL)	3.03 ± 2.06	3.56 ± 1.46
Anthranilic acid (ng/mL)	2.47 ± 2.42	2.51 ± 2.13
Quinolinic acid (ng/mL)	21.1 ± 15.4	22.5 ± 10.9
5-Hydroxyindoleacetic acid (ng/mL)	33.4 ± 12.4	34.4 ± 10.1
Xanthurenic acid (ng/mL)	1.88 ± 1.00	1.13 ± 0.64*
3-Hydroxykynurenine (ng/mL)	2.29 ± 1.47	3.07 ± 0.86
Tryptophan/xanthurenic acid ratio[a]	3.03 ± 1.73	7.83 ± 7.00*,a

Averages are means ± SD. By Mann-Whitney (U) or χ^2 test.
* $p < 0.05$.
[a] Averaged from individual values for tryptophan and XA levels.

Contributors

MC, FF and FN designed the study and wrote the protocol. LL and MS performed the HPLC analysis on serum samples collected. VC and AC recruited and evaluated patients and healthy controls. MC and SF managed the literature searches and analyses. RJB undertook the statistical analysis and reviewed the manuscript, and MC wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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