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Letter to the Editor

Plasma xanthurenic acid in a context of insulin resistance and obesity in schizophrenia

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Dear Editor,

Curto et al. (2019) reported reduced serum xanthurenic acid (XA) levels in ultrahigh risk for psychosis subjects. This finding supports the hypothesis of reduced blood XA levels as a schizophrenia trait marker (Fazio et al., 2015). Notably, XA attenuated hyperactivity induced in mice by the NMDA antagonist MK-801 (Fazio et al., 2015). XA is an 8-hydroxylated analog of kynurenic acid (KYNA), an endogenous NMDA antagonist. Increased KYNA production is causally linked to psychopathology in schizophrenia (Erhardt et al., 2007; Schwarcz et al., 2001). Considering insulin resistance (IR) risk (Pillinger et al., 2017) and association between IR and obesity in schizophrenia, we evaluated plasma levels of XA, KYNA, 3-hydroxykynurenine (3-HK), an immediate XA precursor, and potential associations with IR and obesity in schizophrenia.

Fasting plasma samples were obtained from 52 [19 drug-naïve first-episode (DNFES) and 33 previously-treated, but not medicated for ≥6 weeks] acutely ill DSM-IV schizophrenia patients (Steiner et al., 2017). Fifty-two hospital staff and their relatives' healthy subjects (HS) were matched for gender, body mass index (BMI), and waist circumference (WC) as controls. Kynurenines were evaluated by HPLC–mass spectrometry (Oxenkrug, 2015). IR and obesity markers were previously assessed (Steiner et al., 2017). The study was approved by the University of Magdeburg Review Board and written informed consent was obtained.

Results are presented in Table 1. Plasma levels of XA and KYNA were lower in schizophrenia patients than HS. HOMA-IR was increased but BMI scores were not different between patients and HS. Plasma levels of XA, KYNA and 3-HK were elevated in schizophrenia patients dichotomized into high (≥25; n = 29) and low (<25; n = 23) BMI groups, but no differences were found in HS. However, HOMA-IR and WC were elevated in high versus low BMI subjects in both schizophrenia and HS.

XA (9.13 ± 5.94 and 9.80 ± 5.13, resp.) and 3-HK levels (14.54 ± 5.14 and 15.37 ± 5.89, resp.) were not different between DNFES and previously-medicated patients. KYNA levels were lower in DNFES than in previously-medicated patients (22.85 ± 10.21 and 28.49 ± 11.24, resp., $p < 0.01$). There was no difference in plasma XA, 3-HK and KYNA levels between female (n = 20) and male (n = 32) schizophrenia patients and HS (20 females and 32 males) (data not shown).

XA, KYNA and 3-HK were not correlated with HOMA-IR and insulin in schizophrenia patients although these were correlated in HS. However, kynurenine metabolites did not correlate with fasting glucose levels in both schizophrenia patients and HS (data not shown).

In schizophrenia patients, XA, KYNA and 3-HK were correlated with WC, and 3-HK was correlated with BMI. In HS, levels of XA and 3-HK did not correlate with markers of obesity. In contrast, KYNA was correlated with BMI.

In summary, we have confirmed reduced levels of XA as a trait marker in acutely ill schizophrenia patients compared to controls. Contrary to our findings of positive correlations between plasma XA and markers of IR in controls and previously reported findings in non-schizophrenia subjects with IR and type 2 diabetes patients (Oxenkrug, 2015; Pedersen et al., 2015; Reginaldo et al., 2015), we found no correlation in schizophrenia patients. The diabetogenic effects of XA (e.g., impairment of β-cells insulin biosynthesis and reduced insulin activity via formation of inactive XA-insulin complexes) require increased levels of peripheral XA. However, reduced plasma XA levels in schizophrenia may account for the absence of correlation between plasma XA levels with IR markers in schizophrenia patients.

In contrast, we did find that plasma XA, KYNA and 3-HK levels were correlated with markers of obesity (BMI and WC) in schizophrenia patients. Our observation of elevated XA, KYNA and 3-HK levels in schizophrenia patients with high compared to low BMI might be due to additional XA and 3-HK produced by resident macrophages infiltrating omental adipose, and additional KYNA formed by adipocytes (Favennec et al., 2015). Elevated levels of XA and KYNA, aryl hydrocarbon receptors (AHR) agonists, may contribute to obesity development via overactivation of AHR (Moyer et al., 2016). We did not observe previously reported differential XA or 3-HK levels in controls dichotomized into high and low BMI groups (Theofylaktopoulou et al., 2013). However, the low sample numbers might prevent us from detecting a 2–8% elevation noticed in a larger cohort of overweight non-schizophrenia subjects (Theofylaktopoulou et al., 2013).

Taken together with previously published data, the present results support the suggestion that reduced serum/plasma XA is a schizophrenia trait marker. In addition, we found that XA levels were not influenced by gender or previous exposure to medications although KYNA levels were lower in DNFES. Notably, XA plasma levels were not influenced by severity of IR in schizophrenia patients. However, XA levels in schizophrenia were affected by markers of obesity. These findings suggest the presence of different mechanisms of XA and other downstream metabolites of kynurenine in regulation of body weight in schizophrenia patients and controls.

Contributors

Conception and design of the study: JS, GO, HGB, and PS. Assessment of kynurenines: MvH, JR, and GO. Analysis and interpretation of data: JS, GO, HGB, and PS. First manuscript draft: GO and JS. All authors contributed to and approved the final manuscript.

Declaration of Competing Interest

Prof. P. Summergrad is a non-promotional speaker for CME outfitters, Inc. Other authors have nothing to declare.

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Table 1
Plasma kynurenines and insulin resistance and obesity markers in schizophrenia.

Mean ± SD	XA (nM)	KYNA (nM)	3-HK (nM)	HOMA-IR (mU*mmol/L)	Waist circumference (cm)
HS:					
BMI (25.4 ± 3.8)	12.05 ± 6.15	30.31 ± 12.51	15.07 ± 4.90	0.57 ± 0.38	91.21 ± 11.92
Sz:					
BMI (25.08 ± 4.47)	9.38 ± 4.48[a]	26.43 ± 11.11[a]	14.98 ± 6.12	1.01 ± 1.31[a]	89.2 ± 12.55
HS:					
BMI ≥ 25(27.9 ± 3.23)	11.31 ± 6.04	30.77 ± 8.91	14.87 ± 4.04	0.65 ± 0.43	98.58 ± 9.86
BMI < 25 (22.3 ± 1.7)[b]	13.24 ± 5.69	28.94 ± 17.22	15.55 ± 6.35	0.48 ± 0.38b	81.43 ± 7.13[b]
Sz:					
BMI ≥ 25(29.71 ± 3.04)	11.254.71	30.58 ± 12.92	18.11 ± 6.76	1.71 ± 2.72	101.1 ± 10.01
BMI < 25(21.85 ± 1.63)[b]	8.63 ± 5.53[b]	23.56 ± 9.12b	13.27 ± 4.09[b]	0.88 ± 1.55[b]	81.62 ± 6.84[b]

Spearman's rank correlations: r (*p*-value)	XA	KYNA	3-HK
HS:			
HOMA-IR	**0.31** (0.026)[c]	**0.41** (0.003)[c]	**0.34** (0.001)[c]
Insulin	**0.35** (0.012)[c]	**0.34** (0.015)[c]	**0.30** (0.022)[c]
Sz patients:			
HOMA-IR	0.11 (0.324)	0.08 (0.251)	0.07 (0.352)
Insulin	0.03 (0.427)	0.08 (0.341)	0.06 (0.254)
HS:			
BMI	0.08 (0.243)	**0.28** (0.032)[c]	0.06 (0.186)
Waist circumference	0.12 (0.356)	0.05 (0.432)	0.08 (0.267)
Sz patients:			
BMI	0.07 (0.422)	0.06 (0.513)	**0.32** (0.024)[c]
Waist circumference	**0.32** (0.033)[c]	**0.29** (0.033)[c]	**0.33** (0.020)[c]

Abbreviations: HS — healthy subjects; Sz — schizophrenia patients; XA — xanthurenic acid; KYNA — kynurenic acid; 3-HK — 3-hydroxykynurenine; BMI — body mass index (calculated as weight in kilograms divided by height in meters squared); HOMA-IR — homeostasis model assessment of insulin resistance.
[a] $p < 0.05$ vs HS.
[b] $p < 0.05$ vs BMI > 25 (Mann-Whitney *U* test).
[c] Significant *p*-value.

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