

Peripheral kynurenine-3-monooxygenase deficiency as a potential risk factor for metabolic syndrome in schizophrenia patients

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Abstract

Deficiency of brain kynurenine-3-monooxygenase (KMO), a key enzyme of down-stream metabolism of tryptophan (Trp) derivative, kynurenine (Kyn), shifts KYN metabolism from formation of 3-hydroxyKyn (3-HK) toward production of kynurenic (KYNA) and anthranilic (ANA) acids. Genetically- or pharmacologically-induced KMO deficiency resulted in elevated concentrations of Kyn, KYNA, ANA and decreased 3-HK not only in brain but in serum of experimental animals as well. However, in schizophrenia patients (SP) elevated serum concentrations of ANA and decreased 3-HK were reported without concurrent increase of Kyn and KYNA. Present study found elevated Kyn:Trp ratio (by 20%) and Kyn concentrations (by 30%) in serum of SP with elevated serum KYNA concentrations (by 40%). Elevated serum KYNA and Kyn were reported previously in type 2 diabetes patients and in Zucker Fatty Rats, a model of metabolic syndrome (MetS) suggesting that increased formation of peripheral KYNA and Kyn underlines predisposition of sub-group of SP (and their first-degree relatives) to development of MetS. One of the mechanisms mediating contribution of elevated KYNA and KYN to MetS might be their ability to activate aryl hydrocarbon receptor (AHR), considering that AHR activation promotes induction of MetS in mice fed by Western diet. Evaluation of serum Kyn and its down-stream metabolites might help to identify SP at risk for development of MetS. Modulation of down-stream Kyn metabolism might be a new target for prevention/treatment of MetS in SP

Abbreviations: Trp: Tryptophan; Kyn: Kynurenine; KYNA: Kynurenic acid; ANA: Anthranilic Acid; 3-HK: 3-HydroxyKynurenine; IDO: Indoleamine 2,3-dioxygenase; TDO: Tryptophan 2,3-dioxygenase; KMO: Kynurenine-3-Monooxygenase; KAT: Kynurenine Amino Transferase; Kynase: Kynureninase

Introduction

There are converging evidences of the involvement of tryptophan (Trp) – kynurenine (Kyn) pathway (KP) in pathogenesis of schizophrenia. Kyn is formed from Trp during the initial phase of KP [1]. Further metabolism of KYN is trifurcated into production of 3-hydroxyKyn (3-HK), catalyzed by vitamin B2-dependent Kyn-3-monooxygenase (KMO); kynurenic acid (KYNA) and anthranilic acid (ANA), catalyzed by vitamin B6-dependent Kyn-aminotransferase (KAT) and kynureninase (Kynase), resp.(Fig.1A) [2]. “KYNA hypothesis of schizophrenia” [3] was initiated by a discovery of KMO deficiency in Broadmann area of brain of schizophrenia patients (SP) [4], and was further supported by findings of elevated KYNA concentrations in brains [5] and CSF [6] of SP and by observations of KYNA-induced schizophrenia-like symptoms in experimental animals [7], including disruption of pre-pulse inhibition [8] and impairment of cognitive functions [9], and damage of spinal cord myelin [10] and impairment of oligodendrocyte viability [11]. KMO deficiency increased availability of Kyn as a substrate for unsaturated enzymes, KAT and Kynase, and, therefore, shifts down-stream metabolism of Kyn from formation of 3-HK toward production of KYNA and ANA [1,2]. It was suggested that KYNA contributed to up-regulation of brain dopamine receptors, the hall mark of schizophrenia, via its antagonism to NMDA and $\alpha 7$ -nicotinic acetylcholine receptors [1,3]. Besides the

brain (e.g., glial cells), Kyn, KYNA, ANA, and 3-HK are formed by peripheral tissues (e.g., macrophages, pancreatic cells, adipocytes) [1,12,13]. In experimental studies, KMO deficiency, induced by vitamin B2-deficient diet [14,15] or by knockout of gene, that encodes KMO [16,17], all four markers of KMO deficiency, i.e., elevated Kyn, KYNA and ANA and decreased 3-HK, were observed not only in brain but in serum as well. However, in clinical studies, only elevated ANA and decreased 3-HK concentrations were observed in serum of SP without concurrent increase of Kyn and KYNA [2,18]. Therefore, we were interested to expand our previous study [2] by assessing serum KP metabolites in a subgroup of SP with elevated KYNA.

Materials and methods

Patients

Overnight fasting blood samples from SP (diagnosed according to DSM-V) with serum concentrations of KYNA higher than in controls [2] (three men and four women, age range from 38 to 56 years) were selected for analysis of Kyn and its metabolites. All patients were taking anti-psychotic medication: Abilify (three patients), Haloperidol (two patients) and Haloperidol decanoate injections (two patients).

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Healthy Subjects (Controls)

There were 12 subjects (6 females and 6 males, age range from 32 to 64 years) [2]. Study was approved by Tufts Medical Center IRB.

Assessment of kynurenine metabolites

Serum samples were stored at -50°C until analysis. ANA, Trp, Kyn, KYNA and 3-HK concentrations were analyzed by modified HPLC–mass spectrometry (MS) method as described elsewhere [2].

Statistical analysis

Results are presented as mean \pm standard error (Trp and Kyn in μM and AA, KYNA and 3-HK in nM). Statistical significance was assessed by unpaired t test with Welch correction.

Results and discussion

Serum concentrations of Kyn and its metabolites

KYNA concentrations in studied SP were higher (approximately by 40%) in comparison with controls. Kyn concentrations were elevated by 30%. Kyn:Trp ratio was increased by 20%. There was no statistically significant difference between concentrations of Trp, 3-HK and ANA in SP and controls (Table 1).

Experimental data suggested, at least, four potential clinical markers of KMO deficiency: elevation of KYN, ANA, KYNA and decrease of 3-HK serum concentrations. However, elevated ANA and decreased 3-HK serum concentrations without concurrent elevation of Kyn and KYNA concentrations were reported in SP [2,18]. In the present study of SP with higher than controls KYNA concentration, we observed elevation of serum concentrations of Kyn without concurrent elevation of ANA and decrease of 3HK concentrations. Notably, we observed a significant increase of Kyn:Trp ratio, suggesting activation of Trp conversion into Kyn catalyzed either by inflammation-induced indoleamine-2,3-dioxygenase (IDO) or by stress-induced Trp-2,3-dioxygenase (TDO) [1]. The latter was previously described in prefrontal cortex of SP [19]. Therefore, elevated serum concentration of Kyn (and Kyn:Trp ratio) might be a result of KMO deficiency and/or IDO/TDO activation. Present data and our previous report suggest the existence of, at least, two patterns of peripheral KMO deficiency in SP: elevated ANA with decreased 3-HK (without changes of Kyn and KYNA) (Fig.1B); and elevated Kyn and KYNA (without changes of ANA and 3-HK) (Fig.1C). Peripherally produced Kyn, ANA and 3-HK (but not KYNA) might contribute to central pathology by crossing blood brain barrier (BBB) [20] and entering a pool of centrally formed Kyn metabolites [21]. Increased predisposition of SP to development of Metabolic Syndrome (MetS), e.g., insulin resistance, obesity and dyslipidemia, suggests common signaling pathway between schizophrenia and MetS [22]. Dysregulation of Trp – Kyn pathway was suggested as one of the mechanisms of MetS [23,24,25]

Table 1. Serum concentrations of Kyn metabolites in schizophrenia patients.

	Controls # (n=12)	Schizophrenia (n=7)	P *
Tryptophan(μM)	68.90 \pm 2.49	74.22 \pm 5.28	ns
Kynurenine (μM)	1.76 \pm 0.09	2.32 \pm 0.12	0.02
Kyn x 100: Trp	2.56 \pm 0.35	3.47 \pm 0.20	0.03
3-HK (nM)	19.55 \pm 3.14	11.85 \pm 4.09	ns
KYNA (nM)	35.78 \pm 3.59	49.23 \pm 4.02	0.02
ANA (nM)	21.65 \pm 5.99	63.36 \pm 19.63	ns

#) mean \pm standard error; *) unpaired t test with Welch correction

Abbreviations: KYNA: kynurenic acid; ANA: anthranilic acid; 3-HK: 3-HydroxyKynurenine.

and as a common signaling pathway for schizophrenia and MetS [26] contributing to high prevalence of MetS in schizophrenia. Elevated serum concentrations of KYNA and Kyn, indicative of KMO deficiency, were observed in type 2 diabetes [27–29] and in Zucker Fatty Rats (ZFR), an experimental model of insulin resistance and MetS [30]. KYNA and KYN are endogenous ligands to aryl hydrocarbon receptor (AHR) that regulates xenobiotic-metabolizing enzymes such as aryl hydrocarbon hydroxylase (cytochrome P450) in humans and rodents [31]. AHR over-activation promoted while AHR deficiency protected mice from diet-induced obesity [32,33]. Therefore, peripheral KMO deficiency might contribute to metabolic abnormalities in SP via activation of AHR by increased formation of down-stream Kyn metabolites. Further studies might explore the use of evaluation of serum concentrations of Kyn and its down-stream metabolites to identify SP at risk for development of MetS. Modulation of down-stream Kyn metabolism might be a new target for prevention/treatment of MetS in SP.

Conclusion

KMO deficiency is manifested by elevation of Kyn, KYNA and ANA and decrease of 3-HK in brain and serum of experimental animals. Present results (together with our previously published data) suggest that in serum of SP elevation of KYNA is associated with elevation of KYN (and Kyn:Trp ratio) while elevation of ANA is associated with decrease of 3-HK. Further studies may find clinical correlates of different pattern of KMO deficiency-dependent metabolites in SP. Brain KMO deficiency might contribute to positive and negative symptoms of schizophrenia while peripheral KMO deficiency might underline increased predisposition of SP (and their first-degree relatives) to development of metabolic abnormalities.

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Conflict of interest

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

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