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Increased plasma levels of xanthurenic and kynurenic acids in type 2 diabetes

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Abstract

About 350 million people worldwide have type 2 diabetes (T2D). The major risk factor of T2D is impaired glucose tolerance (pre-diabetes) with 10% of pre-diabetes subjects develop T2D every year. Understanding of mechanisms of development of T2D from pre-diabetes is important for prevention and treatment of T2D. Chronic stress and chronic low grade inflammation are prominent risk factors for T2D development in pre-diabetic subjects. However, molecular mechanisms mediating effect of stress and inflammation on development of T2D from pre-diabetes remain unknown. One of such mechanisms might involve kynurenine (KYN) pathway (KP) of tryptophan (TRP) metabolism. We suggested that chronic stress- or chronic low grade inflammation-induced upregulation of formation of upstream KYP metabolites, KYN and 3-hydroxyKYN, combined with chronic stress or chronic low grade inflammation-induced deficiency of pyridoxal 5'-phosphate, a cofactor of downstream enzymes of KYP, triggers overproduction of diabetogenic downstream KYN metabolites, kynurenic acid (KYNA) and 3-hydroxyKYNA (also known as xanthurenic acid (XA)). As the initial assessment of our working hypothesis, we evaluated plasma levels of up- and down-stream KP metabolites in the same samples of T2D patients. KYN, XA and KYNA levels in plasma samples of T2D patients were higher than in samples of non-diabetic subjects. Our results provide further support of "kynurenine hypothesis of insulin resistance and its progression to T2D" that suggested that overproduction of diabetogenic KP metabolites, induced by chronic stress- or chronic low grade inflammation, is one of the mechanisms promoting development of T2D from pre-diabetes. Downstream metabolites of KP might serve as biomarkers of T2D and targets for clinical intervention.

Keywords

Type 2 diabetes; tryptophan; kynurenines; xanthurenic acid; kynurenic acid; stress; inflammation

Introduction

About 350 million people worldwide have type 2 diabetes (T2D). The major risk factor of T2D is impaired glucose tolerance (pre-diabetes) with 10% of pre-diabetes subjects develop T2D every year. Understanding of mechanisms of T2D development from pre-diabetes is

Conflict of interest. None

important for prevention and treatment of T2D. Stress [1] and inflammation [2] are prominent risk factors for development of T2D in pre-diabetic subjects. However, molecular mechanisms mediating effect of stress and/or inflammation on development of T2D from pre-diabetes remain unknown. Clinical and experimental data on the involvement of tryptophan (TRP) metabolites in pathogenesis of T2D was reviewed in 1985 [3]. Since its publication, new studies revealed the role of chronic stress and chronic low grade inflammation in regulation of kynurenine (KYN) pathway (KP) of tryptophan (TRP) metabolism. TRP, an essential (for human) amino acid, is a substrate for biosynthesis of menthoxyindoles (serotonin, N-acetylserotonin and melatonin). Most of TRP (about 95%) is metabolized along KYN pathway, the major source of NAD in humans [4] (Fig.1). Stress hormones and/or inflammatory factors (e.g., IFNG and LPS) activate up-stream steps of KP, i.e., conversion of TRP into KYN and KYN into 3-hydroxykynurenine (3-HKYN), due to activation of TRP- or indoleamine-2,3-dioxygenases (TDO or IDO), and of KYN-monoxygenase (KMO), resp. [5]. The key enzymes of downstream metabolism of KYN and 3-HKYN require pyridoxal-5-phosphate (P5P) as a co-factor: aminotransferases (KAT), metabolizing KYN into KYNA and 3-HKYN into 3-HKYNA; and kynureninase (KYNase), metabolizing 3-HKYN into 3-HAA [4]. (3H-KYNA was discovered in 1935 and named xanthurenic acid (XA))[6].

Stress hormones (e.g., cortisol) might cause P5P deficiency by activation of P5P phosphatase [7] while inflammation induces P5P functional deficiency because of increased demand for P5P as a co-factor of more than 200 stress or inflammation-induced enzymes [8]. Since KYNase is more sensitive to deficiency of P5P than KAT, P5P deficiency diverts 3-HKYN metabolism from formation of 3-HAA to production of XA, and, consequently, to accumulation of KYN and KYNA, depending on the severity of PLP deficiency [9]. Experimental studies suggested diabetogenic effects of KP metabolites, such as XA-induced hyperglycemia [10], increased urine excretion of XA in rat model of diabetes [11], and impairment of biosynthesis [12] and biological activity of insulin by KYN, XA, KYNA and their derivatives [13, 14]. Thus, chronic stress and chronic low grade inflammation directly activate enzymes of the upstream steps of KP and divert downstream steps of KP (due to P5P deficiency) from biosynthesis of NAD towards formation of diabetogenic downstream metabolites. We proposed that resulting overproduction of diabetogenic KYN, 3H-KYN, 3-HAA, XA and KYNA is one of the mechanisms of chronic stress or chronic low grade inflammation-induced development of T2D in pre-diabetes [15] (Fig.2).

This hypothesis might be further supported by our finding of positive correlation of plasma levels of KYN with severity of insulin resistance (IR), and pancreatic beta-cell function evaluated by homeostatic model assessment (HOMA-IR and HOMA2-B, resp.) in hepatitis C (HCV) virus patients. The importance of this finding is stressed by the four fold increased incidence of IR in HCV [16]. Increased urine excretion of XA was reported in three pre-diabetic [17] and twenty T2D patients [11]. However, we are not aware of studies of both up- and down-stream diabetogenic KP metabolites in the same plasma samples of T2D patients. As an initial step in evaluation of “kynurenine hypothesis of insulin resistance and its progression to T2D” [15], we compared plasma concentrations of TRP, KYN, KYNA, XA and 3-HAA in T2D patients and healthy, non-diabetic subjects (control group).

Methods

Subjects

Patients—Overnight fasting plasma samples were collected from thirty (18 female and 12 male) T2D patients: twenty four Hispanics, four American Caucasians and two African Americans. T2D was diagnosed according to criteria of American Diabetes Association. All patients were taking metformin, 500 mg (16 patients) or 1000 mg/day (14 patients).

Healthy subjects(controls)—There were twenty four subjects (12 females and 12 males): twelve American Caucasians, six Hispanics and six African Americans. Study was approved by Tufts Medical Center IRB.

Determination of kynurenines—Plasma samples were stored at -50°C until analysis. Plasma levels of TRP – KYN metabolites were analyzed by gas chromatography–mass spectrometry method by Brains On-Line LLC, CA, USA.

Statistical analysis—Results are presented as mean $\pm$ standard deviation (TRP and KYN in $\mu\text{M/L}$ and KYNA, XA, 3-HAA in nM/L). Non-parametric tests were used as indicated below.

Results

T2D patients were older (53.8 ± 8.3 years) than control subjects (43.3 ± 10.9 years) ($p=0.01$, Mann-Whitney test, two-tailed).

Glucose levels of T2D patients were 157.87 ± 22.4 mg/dl (range 118 – 182).

Upstream metabolites of TRP – KYN pathway

There were no differences between TRP levels in plasma samples of T2D patients and control subjects (Table 1).

KYN levels were higher in plasma samples from T2D patients than in control subjects (Table 1).

KYN/TRP ratio, a clinical marker of IDO/TDO activity [18], was higher in plasma samples of T2D (2.88) than in samples of control subjects (2.51), although the differences did not achieve statistical significance.

Downstream metabolites of TRP – KYN pathway

XA and KYNA levels were higher in plasma samples of T2D patients than in control subjects (Table 1).

3-HAA levels in plasma samples of T2D patients were lower than in control subjects although difference did not achieve statistical significance (Table 1).

There were no differences between 3-HKYN levels of T2D patients (16.97 ± 7.1) and control subjects (16.72 ± 8.6).

Tryptophan – kynurenine metabolites and metformin

Considering that metformin was reported to elevate plasma levels of TRP [19] and inhibit TDO expression in breast cancer cells under constitutive and inducible conditions[20], we analyzed the potential effect of dose of metformin on studied markers in T2D patients.

Plasma levels of KYN in T2D patients (n=16) treated with 500 mg of metformin were higher than in control subjects (2.64 ± 0.96 and 1.76 ± 0.48 μM /L, resp., $p<0.005$, Mann-Whitney, two-tailed test). Plasma KYN levels of T2D patients treated with 1000 mg of metformin (n=14) had tendency to be slightly higher than controls (2.04 ± 0.23 , $p<0.03$).

Correlations between TRP – KYN metabolites

XA levels were strongly correlated with KYNA in plasma samples of both control subjects and T2D patients (Table 2).

Plasma levels of KYN were correlated with levels of TRP and KYNA in plasma samples of both control subjects and T2D patients (Table 2).

TRP plasma levels were correlated with XA in control subjects but show rather weaker correlation in T2D patients. Correlation between TRP and KYNA was found in control subjects but not in TD patients (Table 2).

There were no correlations between 3-HAA levels and other studied metabolites and between age and levels of all studied metabolites in plasma samples of T2D patients and control subjects (Spearman's Rank, two tailed test) (data not shown).

Glucose levels positively correlated with TRP, KYN, and KYNA (Table 2).

Discussion

Major findings of the present study are the increased plasma levels of KYN and downstream KP metabolites, KYNA and XA, in T2D patients. Increases of KYN/TRP ratio and decreases of 3-HAA plasma levels of T2D did not reach the level of statistical significance.

Previous studies assessed KP metabolites in urine [21], and skin [22] of T2D patients. Serum KYN metabolites were evaluated only in patients with diabetic retinopathy, a complication of both T2D and T1D [23]. None of these studies assessed P5P-dependent KYN metabolites, XA, KYNA and 3-HAA.

The increase of KYN observed in the present study suggests activation of TDO or IDO. This suggestion might be further supported by tendency to increased KYN/TRP ratio, an index of TDO/IDO activity, in T2D patients. Since TDO and IDO could not be activated concurrently [24], increased plasma levels of KYN (and KYN/TRP ratio) might result from either TDO or IDO activation. Inflammatory factors (e.g, IFNG, LPS), but not stress hormones, concurrently with IDO stimulate rate-limiting enzyme of pteridines pathway with consequent formation of neopterin. Assessment of plasma levels of neopterin helps to differentiate between TDO and IDO-induced elevation of KYN [25]. Without assessment of neopterin levels, it is impossible to attribute the observed differences in KYN/TRP ratio to

activation of TDO or IDO. It is noteworthy that we found plasma neopterin levels positively correlated with HOMA-IR and negatively with P5P in 592 participants of study of Adult Boston Community Dwellers of Puerto Rican Origin [26].

Considering that metformin might elevate plasma levels of TRP [19] and inhibit TDO expression [20], one might expect higher TRP and lower KYN levels in patients treated with 1000 mg than 500 mg of metformin. However, we, on contrary, observed higher KYN levels in T2D patients treated with lower (500 mg) dose of metformin. Therefore, present results do not support the notion that metformin increases plasma TRP and inhibits TDO [19, 20]. One might suggest that our data dependent on better control of T2D with higher (1000 mg) than lower (500 mg) dose of metformin. i.e., that KYN plasma levels reflected the severity of pathogenic changes of the disease rather than effect of medication.

As to down-stream KYN metabolites, increased urine excretion of XA was reported in diabetic patients [11] but was not assessed in plasma (or serum) samples. Elevation of serum KYNA, the other P5P-dependent metabolite, was reported in diabetic retinopathy but without assessment of XA [23]. The present study found increased levels of both XA and KYNA in plasma samples of T2D patients. It is noteworthy that correlation between TRP and XA was weaker in T2D patients than in controls while correlation between TRP and KYNA was not detected at all in T2D patients. Such a difference suggests dysregulation of physiological steps of XA and KYNA production. Formation of XA, KYNA and 3-HAA depends on P5P sensitive enzymes. While most experimental studies revealed association of P5P deficiency with decreased production of 3-HAA and increased formation of XA [9], data on effect of P5P deficiency on KYNA production is controversial: decreased [27] and unchanged [28] urinary KYNA excretion was reported in rats and mice fed by P5P-deficient diet [29]. It is noteworthy that, at least, 50% drop of normal cellular P5P concentrations are required to initiate changes in KYN metabolites [9]. In humans, 28 days of a vitamin B-6–deficient diet resulted in increased KYN, XA, and KYNA urine excretion after TRP load [30].

The present data of increased plasma levels of KYN and downstream KP metabolites, KYNA and XA in the same plasma samples of T2D patients might provide further support for “kynurenine hypothesis of insulin resistance (IR) and its progression to T2D” (Fig.2) [15].

The present findings are in agreement with observations of increased plasma KYN, XA, KYNA levels and KYN/TRP ratio and decreased levels of P5P in patients with diabetes in comparison with patients with normal glucose metabolism among subjects with stable angina pectoris [31] that were reported after presentation of our data at ICNA (September, 2014) and submission of this manuscript (November, 2014).

Therefore, dysregulation of KP were observed to associate with IR in HCV patients [17], in diabetic patients with stable angina pectoris [31] and in T2D patients (present report).

Chronic stress or chronic low grade inflammation – induced up-regulation of upstream steps of KP combined with P5P deficiency, resulting in shifting of down-stream KYN metabolism from formation of NAD toward production of diabetogenic KYN derivatives, might

contribute to increased association of IR (and T2D) with aging, neurodegenerative diseases (e.g., Parkinson's, Alzheimer's and Huntington's), and schizophrenia and treatment by antipsychotic medications; viral infections (e.g., HIV and HCV), and depression [32, 33].

Further evaluations of "kynurenine hypothesis of insulin resistance and its progression to T2D" have to consider the limitations of the current study: across-the-board rather than prospective design, relatively small number of samples, not age-, gender- race-matched controls and treatment with metformin. If confirmed, metabolites of KP might be next new biomarkers of IR and T2D, and a new target for prevention and treatment of IR and T2D [34].

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Abbreviations

T2D	type 2 diabetes
IR	insulin resistance
TRP	tryptophan
NAD	nicotinamide adenine dinucleotide
IFNG	interferon gamma
LPS	lipopolysaccharide
KP	kynurenine pathway of TRP metabolism
KYN	kynurenine
KYNA	kynurenic acid
3-HKYN	3-hydroxykynurenine
3-HKYNA	3-hydroxykynurenic acid
XA	xanthurenic acid
3-HAA	3-hydroxyantranilic acid
KMO	kynurenine 3-monooxygenase
P5P	pyridoxal 5'-phosphate
KAT	kynurenine aminotransferase
KYNase	kynureninase
IDO	indoleamine-2,3-dioxygenase
TDO	tryptophan-2,3-dioxygenase
HIV	human immunodeficiency virus
HCV	hepatitis C virus
HOMA	homeostatic model assessment

Fig.1.

Major up- and down-stream steps of tryptophan – kynurenine metabolic pathway

Healthy subjects

T2D

Fig.2.

Dysregulation of tryptophan – kynurenine metabolic pathway in T2D

Table 1

Plasma kynurenines in type 2 diabetes patients

	CONTROLS (n= 24)	T2D (n=30)	P*
Tryptophan (μM /L)	68.9±12.21	80.37±22.50	ns
Kynurenine (μM /L)	1.76±0.48	2.32±0.84	0.01
Xanthurenic acid (nM /L)	11.46±5.40	15.25±5.07	0.02
Kynurenic acid (nM /L)	36.41±14.37	46.09±13.31	0.01
3-hydroxyantranilic acid (nM /L)	23.72±8.82	16.59±4.34	ns

* Mann-Whitney Test, two-tailed

Table 2

Correlations between glucose and kynurenine metabolites in T2D

	TRP	KYN	XA	KYNA	Glucose in T2D
TRP: Control T2D		0.43/0.05* 0.48/0.008	0.85/0.0001 0.44/0.01	0.62/0.004* ns	0.47/0.05
KYN: Control T2D	0.43/0.05 0.48/0.008		ns ns	0.61/0.004 0.62/0.0004	0.56/0.02
XA: Control T2D	0.85/0.0001 0.44/0.01	ns ns		0.74/0.0002 0.62/0.004	ns
KYNA: Control T2D	0.62/0.004 ns	0.61/0.004 0.62/0.0004	0.74/0.0002 0.62/0.004		0.54/0.02
Glucose T2D	0.47/0.05	0.56/0.02	ns	0.54/0.02	

* r/p<, Spearman's Rank Correlation, two-tailed