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Insulin resistance and dysregulation of tryptophan – kynurenine and kynurenine – nicotinamide adenine dinucleotide metabolic pathways

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Abstract

Insulin resistance (IR) underlines aging and aging-associated medical (diabetes, obesity, dyslipidemia, hypertension) and psychiatric (depression, cognitive decline) disorders (AAMPD). Molecular mechanisms of IR in genetically or metabolically predisposed individuals remain uncertain. Current review of literature and our data presents the evidences that dysregulation of tryptophan (TRP) – kynurenine (KYN) and KYN – nicotinamide adenine dinucleotide (NAD) metabolic pathways is one of the mechanisms of IR. First and rate-limiting step of TRP – KYN pathway is regulated by enzymes inducible by pro-inflammatory factors and/or stress hormones. The key enzymes of KYN – NAD pathway require pyridoxal-5-phosphate (P5P), an active form of vitamin B6, as a co-factor. Deficiency of P5P diverts KYN – NAD metabolism from production of NAD to the excessive formation of xanthurenic acid (XA). Human and experimental studies suggested that XA and some other KYN metabolites might impair production, release and biological activity of insulin. We propose that one of the mechanisms of IR is inflammation- and/or stress-induced up-regulation of TRP – KYN metabolism in combination with P5P deficiency-induced diversion of KYN – NAD metabolism towards formation of XA and other KYN derivatives affecting insulin activity. Monitoring of KYN/P5P status and formation of XA might help to identify subjects-at-risk for IR. Pharmacological regulation of the TRP – KYN and KYN – NAD pathways and maintaining of adequate vitamin B6 status might contribute to prevention and treatment of IR in conditions associated with inflammation/stress-induced excessive production of KYN and deficiency of vitamin B6, e.g., diabetes type 2, obesity, cardiovascular diseases, aging, menopause, pregnancy, and hepatitis C virus infection.

Keywords

insulin resistance; tryptophan; kynurenines; xanthurenic acid; vitamin B6; inflammation; stress; interferon

Introduction

Insulin resistance (IR) underlines aging and aging-associated medical (diabetes, obesity, dyslipidemia, hypertension) and psychiatric (depression, cognitive decline) disorders (AAMPD)[1,2]. Molecular mechanisms of IR in genetically or metabolically predisposed individuals remain uncertain. Current review of literature and our data presents the evidences that dysregulation of tryptophan (TRP) – kynurenine (KYN) and KYN –

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nicotinamide adenine dinucleotide (NAD) metabolic pathways is one of the mechanisms of IR. First and rate-limiting step of TRP – KYN pathway is regulated by enzymes inducible by pro-inflammatory factors and/ or stress hormones. The key enzymes of KYN – NAD pathway require pyridoxal-5-phosphate (P5P), an active form of vitamin B6, as a co-factor. Deficiency of P5P diverts KYN – NAD metabolism from production of NAD to excessive formation of xanthurenic acid (XA). Human and experimental studies revealed that XA and some other KYN metabolites might impair production, release and biological activity of insulin.

We propose that one of the mechanisms of IR is inflammation- and/or stress-induced up-regulation of TRP – KYN metabolism in combination with P5P deficiency-induced diversion of KYN – NAD metabolism towards formation of XA and other KYN derivatives affecting insulin activity.

Tryptophan – kynurenine metabolic pathway

Tryptophan (TRP) is an essential (for humans) amino acid. About 5 % of non-protein route of TRP metabolism is utilized for formation of methoxyindoles: serotonin, N-acetylserotonin and melatonin [3, 4] (Fig.1).

The major non-protein route of TRP metabolism is formation of KYN, catalyzed by rate-limiting enzymes: *indoleamine 2,3-dioxygenase* (IDO) or *TRP 2,3-dioxygenase* (TDO) [4]. IDO is activated by pro-inflammatory mediators, e.g., interferon-gamma (IFNG), tumor necrosis factor-alpha, IL-1 beta, and lipopolysaccharide, while TDO is inducible by stress hormones, e.g., cortisol, estrogens, prolactin, and by substrate, TRP [3].

Kynurenine – nicotinamide adenine dinucleotide metabolic pathway

KYN is substrate for two post-KYN metabolic pathways: 1). Formation of kynurenic acid (KYNA), catalyzed by *KYN aminotransferases* (KAT). KYNA is a precursor of quinaldic acid (QA) [5]; and 2). Formation of 3-hydroxyKYN (3-HK) catalyzed by *KYN 3-monooxygenase* [3,4].

3-HK is a substrate for two metabolic pathways: 1). Formation of nicotinamide adenine dinucleotide (NAD). The first step of the 3-HK – NAD pathway catalyzed by *kynureninase*, and 2). Formation of xanthurenic acid (XA), catalyzed by *3-HK-transaminase* [6]. XA is a precursor of 8-hydroxyquinaldic acid (8-HQ) [7].

Pyridoxal 5'-phosphate and KYN – NAD metabolic pathway

Pyridoxal 5'-phosphate (P5P), an active form of vitamin B6, is a cofactor for >100 metabolic reactions, including key enzymes of post-KYN metabolism: *KYN 3-monooxygenase*, *KAT* and *kynureninase*, the latter enzyme is particularly sensitive to dietary vitamin B-6 restriction [8]. Down-regulation of *kynureninase*, caused by P5P deficiency, shifts 3-HK metabolism from formation of NAD to production of XA and KA [9]. P5P deficiency combined with up-regulated TRP conversion to KYN leads to increased availability of 3-HK as a substrate for formation of XA and 8-HQ, and increased availability of KYN as a substrate for KYNA and QA in the cerebellum, corpus striatum, frontal cortex, and pons/medulla [10], blood [11], urine [12], pancreatic islets [13, 14].

Vitamin B6 depletion resulted in drastic increase while vitamin B6 supplementation normalized urinary 3-HK and XA after TRP load in cardiac [15] and obese [16] patients and rats [17]. Therefore, P5P deficiency combined with up-regulation of TRP – KYN pathway

might divert KYN – NAD metabolism towards increased formation of XA at the expense of NAD production (Fig.1).

The other consequence of P5P deficiency-induced down-regulation of *kynureninase* is the decreased formation of NAD that leads to inhibition of synthesis and secretion of insulin and the death of pancreatic beta-cells [18]. Considering that NAD inhibits TDO, decreased formation of NAD caused by P5P deficiency, might lead to further activation of TDO and increased production of KYN) [19].

Besides P5P deficiency, *kynureninase* might be inhibited by XA, thus sustaining the accumulation of 3-HK, KYNA, KYN and XA at the expense of NAD production [20]. Additionally, XA might perpetuate P5P deficiency by inhibiting pyridoxal kinase, the enzyme catalyzing the formation of P5P from vitamin B6 [21].

It is noteworthy that vitamin B6 dose-dependently decreased insulin levels and improved insulin sensitivity in the experimental model of type 2 diabetes [22].

Diabetogenic effects of KYN derivatives

Xanthurenic acid

Increased urine excretion of XA was reported in type 2 diabetes patients in comparison with in healthy subjects [23]. Recent study found the increased levels of XA precursors, KYN and 3-HK in serum samples of diabetic retinopathy patients [24]. XA induced experimental diabetes in rats [25].

The possible mechanisms mediating XA contribution to the development of diabetes might be 1). Formation of chelate complexes with insulin (XA-In). As antigens, XA-In complexes are indistinguishable from insulin but have 49% lower activity than pure insulin [25]; 2). Formation of Zn⁺⁺-ions – insulin complexes in β -cells that exert toxic effect in isolated pancreatic islets [26, 27]; 3). Inhibition of insulin release from rat pancreas [13]; and 4). Induction of pathological apoptosis of pancreatic beta cells through caspase-3 dependent mechanism [27,28].

Kynurenic acid

KYNA was found to be increased in urine of nonhuman primate and mouse models of type 2 diabetes mellitus in a recent metabolomic study [30], and in patients with diabetic retinopathy [24]. KYNA (in micromolar concentrations) was detected in pancreatic juice of pigs [31].

The possible mechanisms of diabetogenic effect of KYNA might be related to KYNA ability to block NMDA receptors. Thus, NMDA antagonist and pharmacological precursor of KYNA, 7-chlorokynurenic acid [4] and NMDA antagonist, MK-801, negated the inhibition of glucose production induced by NMDA agonists injected into dorsal vagal complex in rodents [32].

In addition, XA, KYNA, and their derivatives, QA and 8-HQ, (in millimolar concentrations) inhibit pro-insulin synthesis in isolated rat pancreatic islets [33]

Recent study revealed elevated expression of IDO in serum samples of diabetic retinopathy patients [24]. In the same vein, surplus dietary TRP, the substrate for formation of KYNA and XA, induced IR in pigs [34].

Clinical markers of up-regulation of TRP – KYN pathway

Plasma (serum) ratio of KYN to TRP (KTR) is a generally accepted clinical marker of IDO activity [11]. Considering that both IDO and TDO regulate the rate of TRP conversion into KYN [35], plasma concentrations of TRP and KYN might be affected by the activity of stress hormone inducible TDO as well. However, KTR does reflect IDO activity in conditions associated with inflammation (2).

Concurrently with induction of IDO, pro-inflammatory factors (e.g., IFNG, TNF-alpha, IL-1beta) induce guanosine triphosphate cyclohydrolase I (GTPCH), a rate-limiting enzyme in the biosynthesis of tetrahydrobiopterine (BH4), the obligatory cofactor of nitric oxide (NO) synthase (NOS) [39]. GTPCH catalyzes GTP conversion into 7,8-dihydroneopterin (BH2) [36]. Pro-inflammatory factors-induced activation of GTPCH results in increased formation of neopterin, a stable, water-soluble derivative of BH2 [37]. Therefore, inflammation-induced elevation of neopterin production might be considered not simply a clinical marker of inflammation, but an indirect marker of IDO activation as well [36].

Blood neopterin levels correlate with KTR in healthy humans [38], and cardiovascular patients [11]. We found similar strong ($r=0.68$) and highly significant ($p<0.0001$) correlation between serum KTR ratio and neopterin in 80 hepatitis C virus (HCV) patients treated with interferon-alpha [unpublished data].

Kynurenine/tryptophan ratio, neopterin and P5P levels, and incidence of IR in clinical conditions associated with chronic inflammation and stress

Diabetes

Clinical and experimental data suggest the increased metabolism of TRP in diabetes, resulting most likely, from up-regulation of TRP – KYN pathway. Thus, impaired accumulation of TRP in the brain concomitantly with a much faster disappearance of the administered TRP from the bloodstream was observed in streptozotocin-diabetic rats after TRP load [39]. Similarly, post-loading levels of plasma TRP (but not of other large neutral amino acids) were lower in diabetic patients than in healthy controls. [40]

Recent studies reveal decreased plasma TRP concentrations and increased KYN and KTR in 21 hemodialysis patients with diabetes in comparison with 40 healthy controls patients. An increase in neopterin was correlated with KYN concentrations ($r = 0.393$, $p < 0.01$), suggesting that increased TRP degradation is a result of IDO activation [41]. In the same vein, neopterin but not C-reactive protein, an inflammation marker not related to IDO/GTPCH activation, increased in diabetic in comparison with non-diabetic patients with critical limb ischemia [42].

Decreased kynureninase activity was observed in liver and kidney of alloxan diabetic rabbits [43]. Additionally, XA was identified in pre-diabetes subjects [44].

Neopterin correlated with IR, an early event in the pathogenesis of type 2-diabetes, in Caucasian population [11,45,46]. We observed correlation between plasma neopterin concentrations and IR (HOMA-IR, $r=0.08$, $P < 0.03$), and P5P ($r = -0.13$, $P = 0.002$) in 592 adult (45–75 years of age) participants of community dwellers in the Boston Puerto Rican Health Study. The strongest ($r=0.15$) and most significant ($P<0.0002$) correlation was recognized between HOMA-IR and neopterin/P5P ratio (a combined index of increased inflammation and P5P deficiency) [47]. Low plasma concentrations of P5P have been reported in conditions associated with increased fasting glucose and glycated hemoglobin [48].

Obesity

Obesity represents a major risk factor for the development of IR [49], and is considered an independent cause of IR [50]. In most cases IR exists because of the obesity and will disappear with weight loss [51]. Human obesity is characterized by chronic low-grade inflammation in white adipose tissue that releases many inflammatory mediators, including KYN [52,53]. Serum KTR and IDO expression in omental and subcutaneous adipose tissues and liver were higher in obese than in lean women [54]. KTR and neopterin and inflammatory markers, including C-reactive protein, were increased in morbid obese subjects [55]. However, only neopterin and KTR did not normalize after bariatric surgery and weight loss [55]. These studies suggested that IFNG-induced IDO and GTPCH activities have unique role as the trait (VS state) inflammatory markers in obesity.

P5P deficiency was noted in 11% of morbid obese individuals before laparoscopic sleeve gastrectomy [56]. Significantly lower P5P concentrations were reported in the morbidly obese Norwegian women and men [57].

Depression

The stress-induced TDO activation that shunts TRP metabolism from formation of serotonin towards production of KYN in depression was originally suggested in 1969 [58]. Discovery of inflammation-inducible IDO added another mechanism of up-regulation of KYN formation from TRP in depression [59]. Association of depression with the increased production of cortisol [60] and inflammatory factors [61] are described elsewhere. Both IDO and TDO activation leads to the same major consequences: 1). Deficiency of serotonin (and its metabolites, melatonin and N-acetylserotonin) contributing to insomnia, dysregulation of biological rhythms and impaired neurogenesis observed in depression [62–64]; 2). Up-regulated formation of KYN and its neuroactive derivatives exerting anxiogenic, pro-oxidative and cognitive impairment effects typical for depression [35,65,66].

Increased plasma neopterin levels were reported in depressed patients, further supporting the notion of IDO activation in depression [67]. Low plasma concentrations of P5P have been reported in depression (68). An increase in KTR and a deficiency in vitamin B6 might explain the increased production of XA in depressed patients (69). Although XA levels correlated with the severity of depression (69), elevation of serum XA is not specific for depression but, rather, a marker of P5P deficiency (9,11). However, supplementation with P5P did not normalize elevated XA levels in depressed patients (69).

The increased association between depression and IR (and diabetes) is generally acknowledged [70, 71]. Observation of a 65% increased risk of development of (mostly type 2) diabetes in a prospective study of clinically depressed patients [72] supports the hypothesis that depression leads to diabetes [73].

One of the mechanisms of the increased incidence of IR (and diabetes) in depressed subjects might be a combination of P5P deficiency with the up-regulation of TRP - KYN and dysregulation of KYN – NAD metabolic pathways.

The role of IFNG-inducible IDO in the mechanisms of major depression might be further supported by the strong correlation between increased serum KTR and severity of depression, developed as a side-effect of IFN-alpha treatment of HCV or melanoma patients [74]. We found that presence of high producer (T) allele of IFNG (+874) T/A gene that encodes the production of pro-inflammatory cytokine, IFNG, increases the risk of development of depression during IFN-alpha treatment [75]. Serum neopterin concentrations were higher in HCV versus the non-HCV patient population and predicted resistance to IFN-alpha therapy [76].

Hepatitis C virus

Incidence of IR among HCV patients is 50% that four-fold higher than in non-HCV population [77] HCV infection significantly lowered vitamin B6 [78]. Antecedent HCV infection markedly increases the risk of developing diabetes in susceptible subjects while even non-diabetic HCV patients have IR and specific defects in the insulin-signaling pathway [79]. IFN-alpha treatment was associated with the additional risk of IR (and type 2 diabetes) in comparison with the group of non-viral chronic liver disease [80] or patients with chronic hepatitis B virus [81]. Serum KTR and neopterin concentrations were higher in HCV patients than in non-HCV population [82]. These data are in line with the current hypothesis that increased risk of IR in HCV patients depends on combination of IFNG-induced up-regulation of TRP – KYN metabolism with P5P deficiency-induced dysregulation of KYN – NAD metabolic pathway.

Aging

IR was originally suggested as mechanism of aging by VM Dilman [83–86]. IR is the key factor of aging metabolic syndrome [87]. Aging is associated with vitamin B6 deficiency [88, 89] and increased plasma neopterin and KTR [46, 90]. Up-regulation of TRP – KYN metabolism in aging might results both from activation of IDO due to age-associated chronic inflammation [2] and/or TDO due to age-associated elevation of cortisol production [3, 84].

XA accumulates in organs with aging and activates caspase-9 and -3 leading to apoptosis of pancreatic beta cells [28].

Other conditions associated with insulin resistance

Cardiovascular disease

IR, increased KYN and neopterin production and vitamin B6 deficiency were reported in cardiovascular disease [11, 91,92].

Menopause

Menopause is associated with IR [83,84,93,94]. Production of IFNG, the most powerful activator of IDO, was increased in postmenopausal women [95]. Partial impairment in P5P-dependent kynureninase (suggesting shift to increased production of diabetogenic XA (Fig. 1) was observed in postmenopausal women [90]. This enzymatic activity could be partially restored by vitamin B6 supplementation [96].

Pregnancy and gestations

Up-regulation of TRP–KYN metabolism [97,98] and vitamin B6 deficiency [8] might contribute to the development of gestational diabetes. Administration of vitamin B6 improved oral glucose tolerance in gestational diabetes [99].

Therapeutic interventions

Current hypothesis suggests that prevention and treatment of IR in conditions associated with chronic stress or chronic inflammation should include a combination of vitamin B6 dietary supplementation and pharmacological modifications of TRP – KYN metabolism, aimed on down-regulation of the formation of diabetogenic KYN derivatives. The latter may be achieved by administration of IDO/TDO inhibitors. The known IDO inhibitor, 1-methyl-L-TRY [100] is not available for human use. There are two indirect (via down-regulation of IFNG formation) IDO inhibitors available for human use: minocycline, an antibiotic with anti-inflammatory action [101,102] and antidepressant, wellbutrin [103]. It is noteworthy that wellbutrin, contrary to tricyclic antidepressants, has a favorable metabolic profile [104].

Berberine, isoquinoline alkaloid isolated from *Berberis aristata*, a herb widely used in Indian and Chinese systems of medicine, inhibits IDO significantly stronger than 1-methyl-L-TRY [105] (Table 1). Berberine improves IR in diabetic hamsters [106] and diabetic patients [107,108]. It is noteworthy that both berberine and minocycline prolonged life span and improved health span in *Drosophila* model [109,110]. Consistent with our hypothesis is observation that vitamin B6 supplementation dose-dependently decreased insulin levels and improved IR in KK-A(y) mice, an animal model of obese, type 2 diabetes [111,112].

Conclusions

Review of literature and our data suggests that inflammation or/and stress-induced upregulation of TRP – KYN metabolism, resulting in the excessive production of KYN, is one of the factors predisposing to IR. Deficiency of P5P, a co-factor of the key enzyme of KYN – NAD pathway, diverts the excessive amount of KYN from formation of NAD towards production of XA (and other) diabetogenic derivatives of KYN.

Monitoring of KYN/P5P status and formation of XA might help to identify subjects-at-risk for IR. Pharmacological regulation of the TRP – KYN and KYN – NAD pathways and maintaining of adequate vitamin B6 status might contribute to prevention and treatment of IR in conditions associated with inflammation/stress-induced excessive production of KYN and deficiency of vitamin B6, e.g., diabetes type 2, obesity, cardiovascular diseases, aging, menopause, pregnancy, and hepatitis C virus infection.

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Fig.1.

Vitamin B6 deficiency-induced shift of post-KYN metabolism from biosynthesis of NAD towards formation of diabetogenic KYN derivatives.

Abbreviations. IR – insulin resistance; TRP – tryptophan; IFNG – interferon-gamma; IDO – indoleamine 2,3-dioxygenase; KYN – kynurenine; KMO – KYN-3-monooxygenase; 3-HK – 3-hydroxyKYN; P5P – pyridoxal 5 -phosphate; QUIN – quinolinic acid; NAD – nicotinamide adenine dinucleotide; KYNA – kynurenic acid; XA – xanthurenic acid; QA - quinaldic acid; 8-HQ – 8-hydroxyquinaldic acid; GTP – guanosine triphosphate; GTPCH – GTP cyclohydrolase I; BH2 - 7,8-dihydroneopterin; BH4 – tetrahydrobiopterin; NOS – nitric oxide synthase.

Table 1

The effect of therapeutics and natural products on kynurenine formation from tryptophan.

	berberine	minocycline	wellbutrin
IFNG (production)	?		
IDO (activity)		?	?
TDO (activity)	*	?	?

Abbreviations. IFNG – interferon-gamma; IDO – indoleamine 2,3 - dioxygenase; TDO – tryptophan 2,3 -dioxygenase.

? - no data available;

*
no data available but probable because tryptophan is one of the substrates of IDO (but the only substrate for TDO).