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## Successful metformin treatment of insulin resistance is associated with down-regulation of the kynurenine pathway

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### ABSTRACT

**Context:** An extensive body of literature indicates a relationship between insulin resistance and the up-regulation of the kynurenine pathway, i.e. the preferential conversion of tryptophan to kynurenine, with subsequent overproduction of diabetogenic downstream metabolites, such as kynurenic acid.

**Case description:** We have measured the concentration of kynurenine pathway metabolites (kynurenines) in the brain and pancreas of two young (27 and 28 yrs) insulin resistant, normoglycemic subjects (M-values 2 and 4 mg/kg/min, respectively) using quantitative C-11- $\alpha$ -methyl-tryptophan PET/CT imaging. Both subjects underwent a preventive 12-week metformin treatment regimen (500 mg daily) prior to the PET/CT study. Whereas treatment was successful in one of the subject (M-value increased from 2 to 12 mg/kg/min), response was poor in the other subjects (M-value changed from 4 to 5 mg/kg/min). Brain and pancreas concentrations of kynurenines observed in the responder were similar to that in a healthy control subject, whereas kynurenines determined in the non-responder were about 25% higher and similar to those found in a severely insulin resistant patient. Consistent with this outcome, M-values were negatively correlated with both kynurenic acid levels ( $R^2 = 0.68$ ,  $p = 0.09$ ) as well as with the kynurenine to tryptophan ratio ( $R^2 = 0.63$ ,  $p = 0.11$ ).

**Conclusion:** The data indicates that kynurenine pathway metabolites are increased in subjects with insulin resistance prior to overt manifestation of hyperglycemia. Moreover, successful metformin treatment leads to a normalization of tryptophan metabolism, most likely as a result of decreased contribution from the kynurenine metabolic pathway.

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### 1. Introduction

The insulin resistant (IR) state constitutes the major risk factor for the development of type 2 diabetes (T2D). There is evidence in literature that dysregulation of tryptophan (TRY) metabolism might be one of the mechanisms that contributes to IR [1]. TRY is an essential amino acid that is either incorporated into proteins or undergoes conversion to serotonin (5HT) or to kynurenin (KYN) via the KYN pathway. The KYN pathway is a fundamental mechanism of immunosuppression and peripheral tolerance [2], tightly controlled by the immune system. Extensive body of literature

suggests that chronic stress and/or low-grade inflammation induce an up-regulation of the KYN pathway with subsequent overproduction of diabetogenic downstream metabolites [3]. Experimental studies clearly indicate a diabetogenic effect of KYN pathway metabolites, such as increased kynurenic acid (KYNA) levels in plasma of T2D patients [4] and impairment of biosynthesis/activity [28] of insulin by KYN, KYNA and their derivatives [5]. In addition, as both TRY and KYN readily cross the blood-brain barrier [6], plasma fluctuations of peripheral KYN metabolites directly affect metabolism in the brain KYN pathway. In fact, about 60% of the metabolism along the KYN pathway in the CNS is initiated by KYN crossing the BBB [7]. Consequently, plasma fluctuations of KYN and its metabolites in the periphery directly affect metabolism in the brain KYN pathway, potentially affecting regulatory brain mechanisms that are in control of peripheral glucose

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levels.

Although metformin is one of the safest and most commonly prescribed drugs for treatment of IR, the variability of its therapeutic response is relatively high [8]. The exact mechanism for this differential response is currently unknown. It has been assumed that metformin acts primarily by enhancing the action of insulin in the liver by reducing the rate of hepatic glucose production via inhibition of glycogenolysis and gluconeogenesis. However, this assumption has been recently challenged, instead suggesting that the gut (and especially the distal small intestines) represents the main site of metformin action [9]. Moreover, available data suggests that KYNA is present in high concentration in the lumen of the small intestines (especially in the ileum) and is synthesized from TRY by the gut flora [10]. These new insights implying a possible connection between KYNA and metformin action are the motivation for our study investigating the relationship between regional TRY metabolism and the effect of metformin treatment among normoglycemic subjects with insulin resistance. This is accomplished using PET/CT imaging with [C-11]alpha-methyl-L-tryptophan (AMT) as tracer. AMT is an analogue of tryptophan and has been clinically used for the detection of epileptic tubers, which display increased AMT uptake even in the interictal state [11]. Tissue analysis of resected epileptic tubers demonstrated high concentration of KYN pathway metabolites (especially the concentration of the neurotoxin quinolinic acid [12]), indicating that increased conversion and trapping of AMT in these lesions is due to the up-regulation of the KYN pathway (which is activated in these lesions). More recently, high AMT uptake was demonstrated in gliomas and glioneuronal tumors with high indoleamine 2,3-dioxygenase 1 (IDO-1) expression [13]. Taken together, these results demonstrated that increased AMT uptake in tissue is related to the concentration of KYN pathway metabolites and can be used as a sensitive imaging tool for the quantification of regional levels of KYN pathway metabolites in vivo.

## 2. Subjects and methods

The study was approved by the Wayne State University Institutional Review Board. Written consent was obtained from the participants.

### 2.1. Clinical characteristics (Table 1)

Two healthy, non-diabetic volunteers were included in this study who underwent comprehensive screening tests such as vitals, Body Mass Index (BMI), urinalysis, ECG, body composition, medical/health history, international physical activity questionnaire, and complete blood chemistry, CBC, HbA1c, and lipid profile. After a 10 h fast, subjects underwent a hyperinsulinemic euglycemic clamp (HIEC) study which consisted of a 120min continuous infusion of human regular insulin (Humulin R; Eli Lilly, Indianapolis, IN) that started at a rate of 80 mU/m<sup>2</sup>/min. Euglycemia was targeted for 90 mg/dl by variable infusion of 20% D-glucose. Insulin-stimulated glucose disposal rates (M-value, infusion rate per kg per minute) were calculated as the average value during the final 30min of insulin infusion. After the clamp study, subjects underwent a 12-week preventive intervention with metformin (500 mg/day). After completing the 12 weeks of treatment, the HIEC study was repeated. One subject (MK) responded well to treatment (M-value changed from 1.5 to 12 mg/kg/min after treatment) whereas the other subject (MZ) responded poorly to treatment (M-value changed from 4 to 5 mg/kg/min during the same time period). In addition, two young treatment naïve subjects were included in this study for comparison, one with severe IR (M = 2.0 mg/kg/min) and the other with normal insulin sensitivity (M = 13.0 mg/kg/min).

### 2.2. Imaging procedures

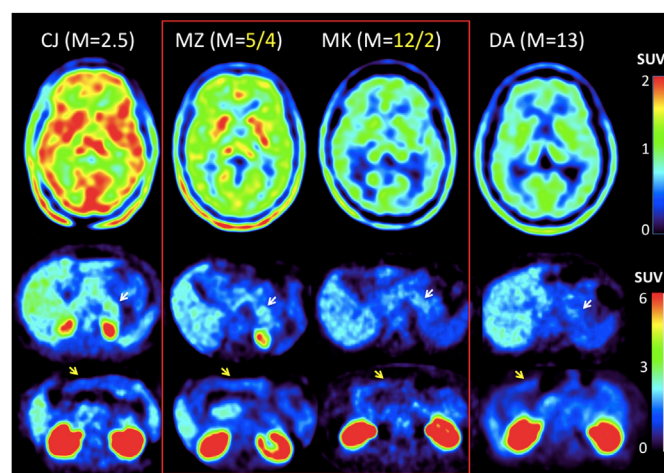
All four subjects underwent <sup>11</sup>C-alpha-methyl-tryptophan (AMT) PET/CT scans of the brain and the abdomen. In addition, structural T1w MR images of the brain were obtained and coregistered with the AMT PET images to guide definition of brain regions. Venous blood was obtained from all subjects yielding plasma values for TRY, KYN, leptin, adiponectin and TNFα. Based on the acquired abdominal CT images, regions were defined in the pancreas and the small intestines. Moreover, using the coregistered T1-w MR images, the following brain regions were defined: lower brainstem (pons and medulla), midbrain, thalamus, caudate and medial prefrontal cortex (mPFC). Regional TRY metabolism was quantified based on the standard uptake value (SUV), which represents AMT tracer concentration (uCi/cc) normalized to the injected activity (mCi) and patient weight (kg).

### 2.3. Laboratory methods

Venous blood was collected into pre-chilled K<sub>2</sub>EDTA vacutainer tubes, and placed on ice. Tubes were centrifuged at 3000 rpm for 10 min at 4 °C, plasma separated and stored at –80 °C until assay. TRY and KYN were determined by HPLC. Adiponectin, Leptin, and TNFα were determined by antibody based assay (AlphaLISA, PerkinElmer), average %CV for replicates were 0.52%, 9.83%, 2.77%, respectively.

## 3. Results

Visual assessment of SUV images (Fig. 1) showed increased concentration of KYN pathway metabolites in the non-responder (MZ) as compared to the responder (MK). This was true for both the brain (Fig. 1, top row) as well as for the pancreas (middle row). For comparison, SUVs determined in a subject with severe IR were found to be highest (CJ, far left column), whereas SUVs in a subject



**Fig. 1.** AMT PET images in subjects with different levels of insulin sensitivity (M-value). Top row shows trans-axial SUV (activity in tissue normalized to injected activity and weight) images at the level of the thalamus, whereas the bottom two rows show SUV images at the level of the pancreas (white arrows) and at the level of the small intestines (yellow arrows). The two subjects who underwent metformin treatment are highlighted in the center (red line), with their post/pre-treatment M-values provided in yellow on top. SUV in the brain and pancreas is higher in subjects with low M-values, consistent with increased conversion of tryptophan via the kynurenine pathway in insulin resistant (CJ and MZ) as compared to insulin sensitive (MK and DA) subjects. The SUV in the small intestines is similar in all 4 subjects (bottom row). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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