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KYNURENNINE AND ITS METABOLITES IN THE RAT WITH EXPERIMENTAL RENAL INSUFFICIENCY

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In uremia a great number of the endogenous metabolites that are ordinarily excreted in urine accumulate in the blood. Among these are the products of KYN degradation. In the present study we evaluated the peripheral KYN metabolism in the various stages of the rat experimental chronic renal insufficiency. Our results showed significant disturbances in peripheral kynurenic pathway, which resulted in the significant decrease of TRP plasma level and augmentation of concentration of its metabolites. The high concentrations of 3-hydroxykynurenine, xanthurenic acid, kynurenic acid, anthranilic acid and quinolinic acid positively correlated with degree of the renal insufficiency. Taking into account the biological properties of KYN metabolites, their accumulation in the blood, may be at least partially, responsible for severity of uremia as well as for uremic symptoms such as neuropathy, increased susceptibility to infections, hypertension, lipid disturbances and anemia.

Key words: kynurenine, 3-hydroxykynurenine, kynurenic acid, xanthurenic acid, anthranilic acid, quinolinic acid, renal failure

INTRODUCTION

Kynurenine (KYN) — the major intermediate product of tryptophan (TRP) metabolism — can be metabolised to a number of substances depending on the extent of the KYN pathway enzymes expression in a particular tissue or cell type (Scheme 1). The family of KYN metabolites includes compounds that have been identified as essential cofactors, neurotransmitter agonists or antagonists (1, 2), neurotoxins (3—5), immunomodulators (1, 6), antioxidants and carcinogens (7).

The kidneys have a dual influence on the TRP metabolism. Firstly, they constitute a major way of its derivatives elimination, most under form of KYN, 3-hydroxykynurenine (3-HKYN), kynurenic acid (KYNA), xanthurenic acid (XA) and quinolinic acid (QA). Secondly, they possess a complex enzymatic system taking part in KYN metabolism (8—12).

In uremia a great number of the endogenous metabolites that are ordinarily excreted in urine accumulate in the blood. Among these are the products of
KYN degradation. Recently, the reduction of TRP and simultaneous increase of KYN and QA concentrations in patients with chronic renal insufficiency was described by Saito et al. (8). On the other hand, it is suggested that accumulation of some KYN metabolites in uremic blood may somewhat be
responsible for uremic symptoms such as, neurological symptoms (13—15), hypertension (16, 17), and anemia (18). Therefore, the kynurenine metabolites seems to play an important role in the development of the kidney failure.

In the present study we evaluated the peripheral KYN metabolism in the various stages of the rat experimental chronic renal insufficiency. We determined plasma levels of KYN and some of its metabolites, i.e. 3-HKYN, AA, KYNA, XA and QA.

MATERIALS AND METHODS

Chemicals

The chemicals were of analytical-reagent grade from MERCK: ammonium acetate, acetic acid, acetonitrile, phosphoric acid, ethylene-di-nitriilo tetra-acetic acid di-sodium salt di-hydrate (EDTA), heptane-1-sulfonic acid sodium salt, di-potassium hydrogen phosphate, potassium di-hydrogen phosphate, tri-sodium citrate di-hydrate; from SIGMA: zinc acetate, potassium phosphate, tri-ethylamine, L-tryptophan, L-kynurenine, kynurenic acid, 3-hydroxykynurenine, anthranilic acid, xanthurenic acid, quinolinic acid, and from BIOVED: pentobarbital.

Animals

Male, normotensive Wistar rats (body weight 180—220 g) were housed in groups of 8—12, under controlled conditions (20°C on 12 hour light/dark cycle). Standard rat chow (LSM — total protein 15.9%) and tap water were available ad libitum.

Surgical induction of uremia

Rats were anesthetized with pentobarbital (40 mg/kg, i.p.). The resection of renal tissue was carried out using the method described by Ormmond and Miller (19). In sham operated rats surgical extraction of the renal capsule was performed. The other experimental groups were as follows: the “moderate” uremia was induced by the removal of the left kidney, while the right kidney was decorticated in 60%; the rats with “severe” uremia were subjected to the same surgical procedure as did “moderate” uremic animals and after 2 weeks the additional 20% of right kidney cortex was removed. The “severe” uremia group of animals was divided in two subgroups “severe” uremia 1 and “severe” 2 uremia. The blood for the biochemical analyses was taken a month after the surgical procedure with exception of the “severe” 2 uremia. In which the blood was collected two months after the last surgical intervention.
Blood sampling

The animals were anaesthetised with pentobarbital (40 mg/kg i.p.) and the blood was drawn by heart puncture and put into a tube containing of 3.13% sodium citrate (citrate/blood = 1/9). The plasma was obtained by a centrifugation of the blood at 3000 rpm for 15 min (temp. 4°C). Samples were stored at –80°C until assayed.

Determination of kynurenine and its metabolites

KYN and its metabolites were determined by high-performance liquid chromatography (HPLC). The chromatographic system was composed of HP 1050 series pump Hewlett-Packard (Germany), Rheodyne injection valve fitted with a sample loop (5 µl) and Waters Spherisorb S3 ODS2 150 × 2.1 mm column (USA). Kynurenine and xanthurenic acid concentrations measured according to Holms (20). Using a HP 1050 series UV detector (Germany) the column effluent was monitored: KYN — 365 nm, XA – 338 nm. The mobile phase consisted of 0.1 M acetic acid, 0.1 M ammonium acetate (pH 4.65) containing 2% of acetonitrile and was pumped at a flow-rate of 0.25 ml/min.

3-HKYN was measured as described by Heyes (21). The column effluent was monitored using a programmable electrochemical detector HP 1049A (Germany). Potential of the working electrode was 0.6 V. The mobile phase consisted of 0.1 M triethylamine, 0.1 M phosphoric acid, 0.3 mM EDTA, 8.2 mM heptane-1-sulfonic acid sodium salt, containing 2% of acetonitrile and was pumped at a flow-rate of 0.25 ml/min.

TRP, KYNA and AA concentrations were determined according to Herve et al. (22). The column effluent was monitored by using an programmable fluorescence detector HP 1046A (Germany). The optimized conditions were determined by recording fluorescence spectra with a stop-flow technique. Excitation and emission wavelengths were set at 254/404 nm for tryptophan and kynurenic acid, 320/420 nm for anthranilic acid. The mobile phase consisted of 50 mM acetic acid, 0.25 M zinc acetate (pH — 4.9), containing 1.2% of acetonitrile was pumped at a flow-rate of 0.25 ml/min.

QA was measured as described by Werner-Felmayer et al. (23). A Phase Separations Partisil 10 SAX 250 × 4.6 mm (USA) column was eluted with 50 mM potassium phosphate (pH — 2.0) containing 12% methanol at a flow rate of 1.8 ml/min. 2 ml of plasma was concentrated on Sep-Pack cartridges (Accell Plus QMA) washed 2 ml water and eluted with 0.2 ml 4 M H₃PO₄ (recovery of spiked quinolinic acid 96%). Using a HP 1050 series UV detector (Germany) the column effluent was monitored (272 nm). The output of the detector was connected to a single instrument LC-2D ChemStation (Germany). Chromatography was carried out at 25°C.
Determination of creatinine and urea

The concentration of creatinine and urea in plasma were measured using commercially available kits: CORMAY CREATININE-30 and CORMAY UREA-30, respectively.

Haematology

Blood was collected from the ventral tail vein into heparinized syringe. Samples were processed in a Hitachi (Japan) counter and the hematocrit, hemoglobin, red cells and blood platelets count were determined.

Statistical analysis

The values are expressed as the mean ± SD; n — represents the number of experiments. Multiple groups comparisons were performed by one-way analysis of variance, and significant differences between groups were assessed by Tukey-Kramer Test. A value of \( p < 0.05 \) was regarded as significant. Correlations were determined using multiple regression analysis and Pearson correlation matrix.

Ethics

The study was submitted to the Ethics Committee of the Medical Academy in Bialystok as being in compliance with the guidelines for care and use of animals physiological science recommended by the National and International law and Guidelines for the Use of Animals in Biomedical Research (Thromb. Haemost. 1987, 58, 1078—1084).

RESULTS

The stage of the experimental chronic renal insufficiency were measured by the concentration of creatinine (CRT), urea (UR) (Tab. 1) and basal haematological parameters: hematocrit (Ht), hemoglobin (Hb), red cells (RBC) and blood platelets count (BP) (Tab. 2).

In the “sham” group the concentration of plasma CRT was 25.3 ± 7.8 \( \mu \)M, and increased to 55.0 ± 10.2 (\( p < 0.05 \)) in “moderate”, to 86.3 ± 26.8 (\( p < 0.001 \)) in “severe” 1, and to 313.6 ± 56.8 (\( p < 0.001 \)) \( \mu \)M in “servere” 2 group. The significant increase in the UR concentration from 3.1 ± 0.7 mM in the “sham” to: 9.3 ± 2.7 (\( p < 0.05 \)), 19.6 ± 7.2 (\( p < 0.01 \)), 85.9 ± 20.9 (\( p < 0.001 \)) mM were noticed in “moderate”, “severe” 1 and 2 group, respectively.
Water (22.6 ± 9.9 ml/day) and food intake (20.7 ± 6.0 g/day) in “sham” group was not altered in “moderate” (26.1 ± 7.3 ml/day and 22.4 ± 5.6 g/day) renal insufficiency rats. In the group “severe” 1 and 2 animals drank similar as did the “sham” group (25.7 ± 4.9 and 27.4 ± 11.7 ml/day, respectively). However, a marked decrease of food intake was observed in these group: 12.6 ± 5.3 (p < 0.01) and 11.0 ± 4.2 (p < 0.001) g/day, respectively.

At the same time, these changes in “moderate” and “severe” 1 and “severe” 2 uremia were associated with the decrease in Ht: from 33.9 ± 0.9% in “sham” to: 29.0 ± 3.1 (p = NS), 26.8 ± 3.1 (p < 0.01), 18.6 ± 4.6 (p < 0.001)% respectively; Hb from 112.1 ± 8.3 g/l in “sham” to: 94.7 ± 13.4 (p < 0.05), 73.0 ± 16.3*** (p < 0.001), 48.1 ± 9.7*** (p < 0.001) g/l, respectively; and RBC from 6.4 ± 0.7 ×10¹²/l to: 6.1 ± 0.7 (p = NS), 5.3 ± 1.0 (p < 0.01), 3.0 ± 0.8 (p < 0.001) ×10¹²/l, respectively. The number of BP significantly decreased only in the group of “severe” 2 uremia 583.0 ± 165.4 ×10⁹/l (p < 0.001) in comparison to “sham” — 949.6 ± 85.9 × 10⁹/l.

**Table 1.** The plasma creatinine and urea concentration of sham-operated rats and varying degrees of experimental renal insufficiency.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>creatinine [μM]</th>
<th>urea [mM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 sham</td>
<td>8</td>
<td>25.3 ± 7.8</td>
<td>3.1 ± 0.7</td>
</tr>
<tr>
<td>2 moderate</td>
<td>12</td>
<td>55.0 ± 10.2*</td>
<td>9.3 ± 2.7*</td>
</tr>
<tr>
<td>3 severe 1</td>
<td>12</td>
<td>86.3 ± 26.8***</td>
<td>19.6 ± 7.3***</td>
</tr>
<tr>
<td>4 severe 2</td>
<td>12</td>
<td>313.6 ± 56.8***</td>
<td>85.9 ± 20.9***</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. Significance of the difference in comparison with the sham-operated group: *p < 0.05, ***p < 0.001.

**Table 2.** The effect of varying degrees of experimental renal insufficiency on erythroid formed elements and count of blood platelets.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>hematocrit [%]</th>
<th>hemoglobin [g/l]</th>
<th>red blood cells count [× 10¹²/l]</th>
<th>platelet cells count [×10⁹/l]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Sham</td>
<td>8</td>
<td>33.9 ± 0.9</td>
<td>112.1 ± 8.3</td>
<td>6.4 ± 0.7</td>
<td>949.6 ± 85.9</td>
</tr>
<tr>
<td>2 moderate</td>
<td>12</td>
<td>29.0 ± 3.1</td>
<td>94.7 ± 13.4*</td>
<td>6.1 ± 0.7</td>
<td>917.4 ± 91.8</td>
</tr>
<tr>
<td>3 severe 1</td>
<td>12</td>
<td>26.8 ± 3.1**</td>
<td>73.0 ± 16.3***</td>
<td>5.3 ± 1.0**</td>
<td>827.4 ± 135.1</td>
</tr>
<tr>
<td>4 severe 2</td>
<td>12</td>
<td>18.6 ± 4.9***</td>
<td>48.1 ± 9.7***</td>
<td>3.0 ± 0.8***</td>
<td>583.0 ± 165.4***</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. Significance of the difference in comparison with the sham-operated group: *p < 0.05, **p < 0.01, ***p < 0.001.
The concentration of TRP in the plasma of “sham” group was 40.3 ± 3.3 μM. In rats with „moderate” and „severe” 1 and 2 uremia the concentration of TRP decreased to 31.3 ± 3.8 (p < 0.01), 23.0 ± 6.1 (p < 0.001), 17.3 ± 4.2 (p < 0.001) μM, respectively (Tab. 3). In contrast TRP metabolite — KYN increased from 1.7 ± 0.3 μM in the “sham” group to 2.5 ± 0.6 (p < 0.05), 2.9 ± 0.7 (p < 0.01), 2.6 ± 0.5 (p < 0.01) μM in „moderate” uremia, „severe” 1 and 2 uremia, respectively. We did not observe any relationship between the increase in the plasma KYN concentration and the stage of the renal insufficiency. The above mentioned dependence was noticed for 3-HKYN — KYN metabolite. In the “sham” group the concentration of 3-HKYN was 51.3 ± 12.0 nM and increased to 77.3 ± 15.6 (p < 0.001), 109.6 ± 22.6 (p < 0.001), 150.5 ± 32.3 (p < 0.001) nM in „moderate” uremia, „severe” 1 and 2 uremia, respectively. According to the Tukey-Kramer statistical test we found significant differences between „moderate” and „severe” 1 uremia (p < 0.01), „moderate” and „severe” 2 uremia (p < 0.001) and „severe” 1 and „severe” 2 uremia (p < 0.001). There was a significant positive correlation between plasma CRT level and 3-HKYN concentration (r = 0.796, p < 0.0001, y = 56.00+0.31x) or UR and 3-HKYN (r = 0.787, p < 0.0001, y = 61.16+1.05x), and negative correlation in relation 3-HKYN to: Ht (r = -0.781, p < 0.0001, y = 37.90-0.11x), to Hb (r = -0.773, p < 0.0001, y = 12.74-0.05x), to RBC (r = -0.786, p < 0.0001, y = 7.84-0.27x).

3-HKYN can be metabolised to XA or through 3-HAA to QA. The plasma concentration of XA was 32.9 ± 8.2 nM and increased to 119.8 ± 29.2 nM (p < 0.001) in „severe” 1 uremia and to 206.8 ± 63.3 nM (p < 0.001) in „severe” 2 uremia. Similarly like in the case of 3-HKYN the relationship

Table 3. The effect of varying degrees of experimental renal insufficiency on concentration of plasma kynurenine metabolites.

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>1 sham</td>
<td>8</td>
<td>40.3 ± 3.3</td>
<td>1.7 ± 0.3</td>
<td>51.3 ± 12.0</td>
<td>32.9 ± 8.2</td>
<td>0.35 ± 0.19</td>
<td>48.9 ± 15.2</td>
<td>54.3 ± 15.0</td>
</tr>
<tr>
<td>2 moderate</td>
<td>12</td>
<td>31.3 ± 3.8**</td>
<td>2.5 ± 0.6*</td>
<td>77.3 ± 15.6*</td>
<td>45.3 ± 15.3</td>
<td>0.98 ± 0.30*</td>
<td>51.4 ± 19.2</td>
<td>42.8 ± 12.8</td>
</tr>
<tr>
<td>3 severe 1</td>
<td>12</td>
<td>23.0 ± 6.1***</td>
<td>2.9 ± 0.7*</td>
<td>109.6 ± 22.6***</td>
<td>119.8 ± 29.2***</td>
<td>1.21 ± 0.26**</td>
<td>159.5 ± 50.5***</td>
<td>232.3 ± 47.8***</td>
</tr>
<tr>
<td>4 severe 2</td>
<td>12</td>
<td>17.3 ± 4.2***</td>
<td>2.6 ± 0.5*</td>
<td>150.5 ± 32.3***</td>
<td>206.8 ± 63.3***</td>
<td>2.11 ± 0.61***</td>
<td>395.4 ± 80.0***</td>
<td>380.0 ± 88.0***</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. Significance of the difference in comparison with the shame-operated group: *p < 0.05, **p < 0.01, ***p < 0.001.
between the increase in the plasma CRT and XA concentration were observed (r = 0.814, p < 0.001, y = 37.25+0.53x) and UR and XA concentration (r = 0.783, p < 0.0001, y = 47.02+1.74x), and negative correlation in relation XA to Ht (r = -0.861, p < 0.001, y = 37.25-0.53x), XA to Hb (r = -0.789, p < 0.0001, y = 11.25-0.03x), XA to RBC (r = -0.766, p < 0.0001, y = 6.91-0.02x).

The significant increase in the concentration of QA from 0.35 ± 0.19 μM in “sham” group to 0.98 ± 0.30 (p < 0.05), 1.21 ± 0.26 (p < 0.001), 2.11±0.61 (p < 0.001) μM in „moderate”, „severe” 1 and 2 uremia were also seen. Additionally, the relationship between the increase in the plasma QA concentration and the stage of the renal insufficiency were observed („moderate” uremia vs „severe” 2 uremia, p < 0.001; „severe” 1 uremia vs „severe” 2 uremia, p < 0.001). Multiple regression analysis demonstrated that there was a linear correlation between CRT plasma concentration and level of QA (r = 0.829, p < 0.0001, y = 0.56+0.02x) or UR – QA (r = 0.846, p < 0.0001, y = 0.75+0.04x), and negative correlation QA with Ht level (r = -0.827, p < 0.0001, y = 33.7-3.01x), QA – Hb (r = -0.833, p < 0.001, y = 11.02-1.28x), QA – RBC (r = 0.709, p < 0.001, y = 6.63-0.62x).

Besides the described above pathways of KYN metabolism, it can be also independently transform to the KYNA and AA. The plasma concentration of KYNA in the “sham” group was 48.9 ± 15.2 nM and increased significantly to 159.5 ± 50.5 (p < 0.001) and 395.4 ± 80.0 (p < 0.001) nM in „severe” 1 uremia and „severe” 2 uremia, respectively. The AA concentration in the “sham” group was 54.3 ± 15.0 nM and increased significantly to 232.3 ± 47.8 (p < 0.001) and 380.0 ± 88.0 (p < 0.001) nM in „severe” 1 uremia and „severe” 2 uremia, respectively. The concentration of KYNA and AA depended on the stage of renal insufficiency: „severe” 1 uremia vs „severe” 2 uremia (p < 0.001). The CRT concentrations positively correlated with KYNA and AA (r = 0.893, p < 0.0001, y = 26.68+1.13x and r = 0.845, p < 0.0001, y = 41.52+1.08, respectively) or UR with KYNA and AA (r = 0.944, p < 0.0001, y = 42.96+4.13 and r = 0.835, p < 0.0001, y = 59.42+3.66, respectively). In turn, KYNA negatively correlated with hematological parameters: Ht, Hb, RBC (r = -0.701, p < 0.001, y = 32.62-0.03x; r = -0.800, p < 0.0001, y = 10.78-0.02x; r = -0.791, p < 0.0001, y = 6.67-0.01x, respectively). Similarly like in the case of KYNA the relationship between AA concentration and Ht, Hb, RBC were observed (r = -0.744, p < 0.001, y = 33.07-0.03x; r = -0.824, p < 0.0001, y = 10.93-0.05x; r = -0.804, p < 0.0001, y = 6.74-0.01x).

**DISCUSSION**

We used animal model of different degrees of renal insufficiency (by partial ablation of the renal parenchyma): “mild, moderate, severe”. The course of
experimental renal failure was monitored by means of the plasma concentration of CRT and UR, both of which increased proportionally to the extent of renal tissue resection. In addition, we evaluated basal hematological parameters (Hb, Ht, RBC), as parameters accompany of the progression of renal insufficiency. We found that they were significantly decreased depending on the stage of the experimental chronic renal insufficiency.

The present study clearly demonstrates decrease of TRP plasma concentration in animals with experimental renal failure, and simultaneous increase of its metabolites content, i.e. KYN, 3-HKYN, KYNA, anthranilic (AA), 3-hydroxyanthranilic (3-HAA), xanthurenic (XA) and quinolinic (QA) acids.

The plasma concentration of KYN and its metabolites depends on TRP supply with food, the activity of specific enzymes as well as its urine elimination (8, 10). The animals had permanent, unlimited access to the granulated food and the tap water. Water and food intake was not altered after the surgical procedure in “moderate” uremic rats in comparison with “sham” group. In the group of “severe” 1 and 2 renal insufficiency animals drank similar as did the “sham” rats. However, a marked decrease in the quantity of consumed rat chow amounts of water was observed in these groups. According to Holmes et al. (10), the decrease in TRP concentration in uremia is multifactorial, including diminished absorption of food TRP, transformation of TRP in bowel epithelium to other indoles competing for binding to proteins, glomerular hyperfiltration typical for initial uremia, or diminished reabsorption of the amino acid in renal tubules. It is possible also, that dietary TRP intake was partially reduced, this case together with mentioned above factors, resulted decrease the plasma concentrations of this amino acid.

The increase in the plasma KYN concentration and the reduction in the plasma TRP level in rats with chronic renal failure are also consistent with the induction of enzymes involved in TRP degradation (8). It is known, that TRP could be metabolised via two pathways. In physiological conditions it is transformed to formylkynurenine by L-tryptophan 2,3-dioxygenase (TDO), whereas in pathology (infections or metabolic disorders) indoleamine 2,3-dioxygenase (IDO) is the main enzyme responsible for TRP degradation (24). Opposite to TDO, IDO is present in all tissues except of hepatocytes. Recently, the increase of TDO activity in chronic renal insufficiency was described by Saito et al. (8).

In the “moderate”, “severe” 1 and 2 groups KYN increased similarly, by about 50% in comparison to the control group. There are only a few publications indicating participation the KYN in the pathomechanism of mesangio-proliferative glomerulonephritis, mainly by impairing the function of glomerular epithelial and endothelial cells (25). The increase in KYN concentration in uremic animals may result from both its enhanced synthesis and diminished clearance. Saito et al. (8) have demonstrated that renal 24-h clearance in KYN was slightly decreased, total urinary excretion of KYN was
increased. Therefore, the accumulation of KYN in renal insufficiency was not mainly related to a decrease of excretion but to a decrease in KYN and/or combined with an increase production.

The kidney tissue uptakes KYN and its toxic metabolite 3-HKYN from circulating blood, and after metabolism, excretes them in to the form of KYNA and XA respectively (26). In our study we demonstrated the significant increase in 3-HKYN and XA in animals with experimental renal failure. In contrast to KYN, the relationship between the increase in the plasma 3-HKYN, XA concentrations and the stage of renal mass reduction was observed. Interesting, that toxicity of 3-HKYN (accumulation of hydrogen peroxide and hydroxyl radical, leading to the cells death) Okuda et al. (4) observed in neuronal cell cultures in similar concentrations, which we found in plasma of “severe” 1 and 2 of renal insufficiency.

Besides the described above pathway of KYN metabolism, it can be independently also transform to the KYNA and AA. The plasma concentration of both, KYNA and AA significantly increased in experimental uremia, and similarly to 3-HKYN positively correlated with the plasma concentration of CRT or UR and negative correlation we observed with some hematological parameters. In animals, it was demonstrated that the kidneys content of KYNA is the highest among all other tissues (11, 27). It has been demonstrated, that KYNA is the main metabolite excreted by tubular secretion. In renal failure this mechanism is considerably impaired, which in consequence may lead to the excessive accumulation of this substance in the blood.

Among the KYN pathway products, the principal one is QA. In this study we observed marked increase the plasma concentration of QA in animals with uremia. The level of this substance dependent on the stage of renal insufficiency. In the “severe” 2 group this level was about 10 times higher than in the control animals. Additionally the plasma concentration of QA negatively correlated with Ht, Hb, RBC. It is worth mentioning that the high QA concentration might lead to a number of disturbances, both in the central nervous system and in peripheral tissues (3, 28, 29). QA is a specific NMDA receptor agonist, and its activation could discontinue of cellular metabolic processes and cell degradation by means of apoptosis or necrosis (13, 24, 30).

It has been also proved that NMDA receptors, due to their function, are crucial for the neurodegenerative processes. Thus it can be suggest that QA may play a role in pathomechanism of anemia in uremic patients (18). However, up to date there are no data concerning a presence of NMDA receptors in the kidney, such a mechanism of kidney damage can not be excluded.

In conclusion, our results showed significant disturbances in peripheral kynurenic pathway, which resulted in the significant decrease of TRP plasma level and augmentation of concentration of its metabolites. The high concentrations of 3-HKYN, AA, KYNA, XA and QA positively correlated
with degree of the renal insufficiency and negatively correlated with some hematological parameters e.g.: Ht, Hb and RBC. Talking into account the biological properties of KYN metabolites, their accumulation in the blood, may be at least partially, responsible for severity of uremia as well as for uremic symptoms such as neuropathy, increased susceptibility to infections, hypertension, lipid disturbances and anemia.

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