Mechanism of increases in L-kynurenine and quinolinic acid in renal insufficiency

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Am J Physiol Renal Physiol 279: F565–F572, 2000.—Marked increases in metabolites of the L-tryptophan-kynurenine pathway, L-kynurenine and quinolinic acid (Quin), were observed in serum and cerebrospinal fluid (CSF) of both the rat and human with renal insufficiency. The mechanisms responsible for their accumulation after renal insufficiency were investigated. In patients with chronic renal insufficiency, elevated levels of serum L-kynurenine and Quin were reduced by hemodialysis. In renal-insufficient rats, Quin and L-kynurenine levels in serum, brain, and CSF were also increased parallel to the severity of renal insufficiency. Urinary excretion of Quin (3.5-fold) and L-kynurenine (2.8-fold) was also increased. Liver L-tryptophan 2,3-dioxygenase activity (TDO), a rate-limiting enzyme of the kynurenine pathway, was increased in proportion to blood urea nitrogen and creatinine levels. Kynurenine 3-hydroxylase and quinolinic acid phosphoribosyltransferase were unchanged, but the activities of kynureninase, 3-hydroxyanthranilate dioxygenase, and aminocarboxymuconate-semialdehyde decarboxylase (ACMSDase) were significantly decreased. Systemic administrations of pyrazinamide (ACMSDase inhibitor) increased serum Quin concentrations in control rats, demonstrating that changes in body ACMSDase activities in response to renal insufficiency are important factors for the determination of serum Quin concentrations. We hypothesize the following ideas: that increased serum L-kynurenine concentrations are mainly due to the increased TDO and decreased kynureninase activities in the liver and increased serum Quin concentrations are due to the decreased ACMSDase activities in the body after renal insufficiency. The accumulation of CSF L-kynurenine is caused by the entry of increased serum L-kynurenine, and the accumulation of CSF Quin is secondary to Quin from plasma and/or Quin precursor into the brain.

More than 90% of L-tryptophan present in the blood is metabolized in the liver under physiological conditions (2). L-Tryptophan is metabolized to L-kynurenine and subsequently to acetyl-CoA and NAD via the kynurenine pathway in which L-tryptophan 2,3-dioxygenase (TDO) acts not only as the first metabolizing liver enzyme but also as the rate-limiting enzyme for L-tryptophan (Fig. 1). It has been reported that abnormalities in L-tryptophan metabolism, such as reductions in total serum L-tryptophan and either increased or unaltered free L-tryptophan concentrations, have been shown in patients with renal insufficiency (10, 38, 39). Furthermore, patients suffering from uremia and encephalopathy due to renal insufficiency have elevated cerebrospinal fluid (CSF) L-tryptophan and 5-hydroxyindoleacetic acid and increased concentrations of regional brain serotonin, a neurotransmitter formed from L-tryptophan (15, 16, 18, 37). The effect of renal insufficiency on L-tryptophan-kynurenine pathway metabolites such as L-kynurenine and quinolinic acid (Quin), however, has not been explored extensively. Quin is an endogenous excitotoxic agonist of N-methyl-D-aspartate (NMDA) receptors (26, 34) and may thereby modulate the effects of excitotoxins. L-Kynurenine at high concentration may induce convulsants (19). Therefore, the effects of kynurenine pathway metabolism have recently focused on the central nervous system (13, 14, 31). In addition, Quin is a cation chelator and an inhibitor of both hepatic phosphoenolpyruvate carboxykinase and gluconeogenesis (21). Quin may also inhibit cardiac contractility (3) and may initiate lipid peroxidation in brain (27). Quin is an important substrate for the synthesis of nicotinamide-containing nucleotides, particularly in case of restricted niacin availability (2). Therefore, accumulation of L-tryptophan-kynurenine pathway metabolites in certain circumstances may be of functional and clinical significance.

In this study, we measured L-kynurenine and Quin concentrations in serum and CSF, and liver TDO, kynureninase, kynurenine 3-hydroxylase, 3-hydroxyanthranilate dioxygenase (3-HAD), quinolinic acid...
phosphoribosyltransferase (QPRT), and aminocarboxymuconate-semialdehyde decarboxylase (ACMSDase) using renal-insufficient rats. We also determined serum L-kynurenine and Quin levels in both healthy subjects and patients with hemodialysis suffering from renal insufficiency.

METHODS

Materials

L-Tryptophan, L-kynurenine, Quin, hexafluoroisopropanol, methylene blue, ascorbic acid, hematin, and TCA were obtained from Sigma (St. Louis, MO). Trifluoroacetylimidazole was obtained from Pierce Chemical (Rockford, IL). Catalase was obtained from Boehringer Mannheim Biochemicals (Indianapolis, IN). Other chemicals, of analytic grade, were purchased from Wako Pure Chemical Industries (Osaka, Japan).

Human Samples

Twenty-one patients with renal failure who were maintained by regular hemodialysis (4 h, 2–3 times/wk) and seven healthy subjects were studied. The mean duration of hemodialysis was 6.3 ± 1.0 yr. Details on age, sex, and results of clinical parameters in renal-insufficient patients have been summarized in Table 1. Blood of healthy control patients was drawn in the morning after overnight fasting. Samples from patients were drawn pre- and posthemodialysis. Before the experiments, informed consent was obtained from each subject.

Table 1. Comparison of clinical parameters between healthy subjects and renal-insufficient patients with hemodialysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Subjects</th>
<th>Prehemodialysis</th>
<th>Posthemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>50.2 ± 18.8</td>
<td>56.4 ± 15.5</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/4</td>
<td>14/7</td>
<td></td>
</tr>
<tr>
<td>Serum albumin, g/dl</td>
<td>4.7 ± 0.4</td>
<td>3.3 ± 0.1*</td>
<td>3.9 ± 0.2†</td>
</tr>
<tr>
<td>Serum urea nitrogen, mg/dl</td>
<td>14.0 ± 2.1</td>
<td>70.8 ± 3.4*</td>
<td>24.2 ± 1.7†</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>1.0 ± 0.2</td>
<td>11.5 ± 0.5*</td>
<td>4.7 ± 0.3†</td>
</tr>
<tr>
<td>Serum L-tryptophan, μmol/l</td>
<td>48.0 ± 5.0</td>
<td>21.6 ± 1.6*</td>
<td>25.2 ± 3.2*</td>
</tr>
</tbody>
</table>

Values are means ± SE of 11 healthy subjects and 21 patients with renal insufficiency. M, males; F, females. *P < 0.01, significantly different from healthy subjects. †P < 0.01, significantly different from patients with renal failure in prehemodialysis value, as determined using ANOVA followed by Fisher's least significant difference multiple comparison matrix.
Experimental Animals

Male Wistar rats (180–220 g) were obtained from Japan SLC (Hamamatsu, Japan). Animals were housed in Plexiglas cages for at least 7 days before study on a 12:12-h dark-light cycle. Food and water were allowed ad libitum throughout the acclimatization and study periods. All experiments were performed according to the guidelines for animal experiments of the Gifu University School of Medicine.

Renal insufficiency was induced by the two-stage surgical procedure of Ormrod and Miller (25, 35). Briefly, in the initial operation, a midline abdominal incision was made, and either 1/3 or 2/3 of the left kidney was excised according to the severity of renal insufficiency desired. Seven days later, a right total nephrectomy was performed resulting in a 2/3 (mild renal insufficiency, n = 6) or 5/6 (severe renal insufficiency, n = 7) nephrectomy. Control rats were sham operated (n = 7). To collect CSF, rats were anesthetized by an intraperitoneal injection of pentobarbital sodium (40 mg/kg) 10 days after the second operation and were placed in a Kopf stereotaxic frame with the head tilted down at ~45°. A 30-gauge needle attached to a 10-cm length of PE-10 tubing and a 1-ml syringe were inserted into the cisternal space. CSF was withdrawn and transferred to a tarred polypropylene tube (29). Blood was collected into syringes from the abdominal vena cava. Serum was isolated by low-speed centrifugation. Afterward, the brain and liver were removed and placed in polypropylene bags. To collect urine, rats were placed in individual metabolic cages for a 24-h period. All samples were stored at ~80°C until analysis.

Biochemical Techniques

Quantification of kynurenine pathway metabolites. Quin was quantified by an electron capture negative chemical ionization gas chromatography/mass spectrometry assay (11) modified as follows: serum and CSF were mixed with 300 µl of deionized water containing 30 pmol [3H]Quin as the internal standard and freeze-dried. Tissue samples were sonicated in 10 vol of ice-cold 1 mol/l hydrochloric acid containing 12 pmol/ml [3H]Quin as the internal standard. Quin standards were treated exactly like the samples. Tissue extracts and Quin standards were washed with 3 ml of chloroform, and the aqueous layers were freeze-dried overnight. Quin and [3H]Quin were derivatized to their dihexafluoroisopropanol esters with complete retention of the isotopes, washed with 250 µl of water, and extracted in 300–600 µl of heptane. They were quantified using a Hewlett-Packard 5988 mass spectrometer operated in the electron capture negative chemical ionization mode using methane as the reagent gas (0.5 Torr). Aliquots of each sample were injected in a 1 × 0.53-mm-ID fused silica precolumn (on-column injection at 80°C) that had been sealed to a 15 m × 0.25-mm-ID DB5 analytical column (J & W Scientific, Folsom, CA). Column temperature was kept at 112°C, and helium was used as the carrier gas. The molecular anions of Quin [mass-to-charge ratio (m/z) 467] and the [3H]Quin internal standard (m/z 470) were monitored, and each peak area at the appropriate retention time was measured for quantification. All quantification was done at a signal-to-noise ratio of ≥20:1. L-Kynurenine was quantified in serum and acidified tissue extracts (1 mol/l perchloric acid) by HPLC assay modified as follows (30): the mobile phase consisted of 2.5% acetonitrile in 0.1 M sodium acetate (pH 4.1), and the mobile phase was filtered through a 0.45-µm HA-type filter obtained from Milipore (Bedford, MA). The flow rate of 0.75 ml/min was maintained throughout the chromatographic run, and the column was a 2-µm 4.6 × 100-mm Super ODS (TOSOH, Tokyo, Japan).

Measurements of serum total protein, albumin, blood urea nitrogen, and creatinine. Total protein, blood urea nitrogen, and creatinine in the serum were measured by the standard method using an automatic Hitachi (Tokyo, Japan) 736 analyzer. The serum albumin concentration was determined using the Wako albumin B test kit (Wako Pure Chemical Industries). Urine albumin and blood cortisol concentrations were determined by enzyme immunoassay, and blood glucagon concentration was determined by RIA.

Enzyme assays. Brain, lung, and liver were disrupted by a Polytron in 3–8 vol of ice-cold 0.14 M KCl/20 mM potassium phosphate buffer (pH 7.0). Homogenates were centrifuged at 105,000 g for 20 min at 4°C. Indoleamine 2,3-dioxygenase, TDO, kynurenine 3-hydroxylase, kynureninase, 3-HAD, QPRT, and ACMSDase activities were measured as described previously (32, 36). Enzyme activity was calculated from the difference between product content both before and after incubation and was expressed as the amount formed per hour per gram wet tissue weight.

Statistical Analyses

Intergroup comparisons were analyzed first by one-way ANOVA, followed by post hoc multiple comparison analysis with Fisher’s least-significance test. Comparisons between a single pair of control and experimental results were performed using the t-test. Correlations were determined using multiple-regression analysis and the Pearson correlation matrix with Bonferroni-adjusted probabilities. All statistical analyses were performed using computer programs (7, 9). Values presented are means ± SE. The numbers of rats or samples are referred to as “n” and are specifically stated in legends for Figs. 1–5 and Tables 1–5.

RESULTS

Effect of Human Renal Insufficiency on Kynurenine Pathway Metabolism

The clinical parameters of renal insufficiency (serum creatinine, urea, and albumin) in both healthy control subjects and renal-insufficient patients are summarized in Table 1. Serum total l-tryptophan levels in renal-insufficient patients before hemodialysis were significantly decreased by ~55% compared with that of healthy control subjects (Table 1). However, no significant differences in total l-tryptophan were observed between pre- and posthemodialysis.

In renal-insufficient patients, serum l-kynurenine and Quin levels in prehemodialysis were significantly increased in all samples compared with the mean value of healthy subjects (Fig. 2). Serum l-kynurenine and Quin levels posthemodialysis were significantly decreased by ~30 and 75%, respectively, compared with values prehemodialysis (Fig. 2).

Effect of Experimental Rat Renal Insufficiency and Administration of ACMSDase Inhibitor on Kynurenine Pathway Metabolism

Both mild and severe cases of renal-insufficient rats had significantly increased blood urea nitrogen, creatinine, and glucagon compared with the sham control group (Table 2). Serum total l-tryptophan levels in the
severe case of renal insufficiency in rats were significantly decreased by ~22% compared with control values (Table 2).

Significantly increased serum L-kynurenine and Quin levels were observed in mild and severe cases of renal-insufficient rats (Fig. 3). There was a significant correlation between serum L-kynurenine and Quin concentrations in renal-insufficient rats ($r = 0.549$, $P < 0.05$). Parallel increases in both L-kynurenine and Quin concentrations in CSF were observed with both groups of renal insufficiency (Fig. 4). Significant increases in L-kynurenine and Quin levels in the cerebral cortex, hippocampus, striatum, thalamus, cerebellum, and CSF were observed in severe case of renal-insufficient rats (Table 3). There was no significant difference in the magnitude of these increases among the different brain regions examined.

Liver TDO activity in renal-insufficient rats was increased by 79% compared with that of sham-oper-
ated animals (Table 4). No significant change in lung indoleamine 2,3-dioxygenase activity was observed (data not shown). Multiple regression analysis demonstrated that there was a linear correlation between liver TDO activities and both serum creatinine ($r = 0.845$, $P < 0.01$) and blood urea nitrogen ($r = 0.714$, $P < 0.01$) in the renal-insufficient group. In addition, although kynurenine 3-hydroxylase and QPRT activities in the liver did not differ between sham control subjects and renal-insufficient rats, the activities of kynureninase, 3-HAD, and ACMSDase were significantly decreased by 37, 30, and 44% below control levels (Table 4). Although serum concentrations of L-kynurenine and Quin in this model were elevated by three times, their renal clearance values were slightly decreased by 19 and 20%, respectively, compared with control subjects. Because urinary excretion of L-kynurenine and Quin also increased (Table 5), it is likely that increased solute concentration is not related to a decrease of renal excretion but to an increase in production and a decrease in degradation.

Although administration of pyrazinamide, an ACMSDase inhibitor, produced a marked increase in serum Quin concentrations, only a small increase in CSF Quin concentrations was found (Fig. 5). No changes of L-kynurenine concentrations in either serum or CSF were observed in the pyrazinamide-administrated rats compared with control subjects.

### Table 3. Regional brain L-kynurenine and Quin concentrations in control and renal-insufficient rats

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Metabolites</th>
<th>Control</th>
<th>Renal insufficiency</th>
<th>Control</th>
<th>Renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L-Kynurenine, nmol/g</td>
<td>0.44 ± 0.01</td>
<td>0.69 ± 0.10*</td>
<td>40 ± 15</td>
<td>145 ± 65*</td>
</tr>
<tr>
<td>Cerebral cortex</td>
<td></td>
<td>0.45 ± 0.14</td>
<td>0.60 ± 0.08*</td>
<td>25 ± 4*</td>
<td>103 ± 42*</td>
</tr>
<tr>
<td>Hippocampus</td>
<td></td>
<td>0.29 ± 0.04</td>
<td>0.64 ± 0.09*</td>
<td>34 ± 6</td>
<td>124 ± 38*</td>
</tr>
<tr>
<td>Striatum</td>
<td></td>
<td>0.47 ± 0.12</td>
<td>0.73 ± 0.09*</td>
<td>47 ± 8</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td>0.48 ± 0.10</td>
<td>0.83 ± 0.11*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE of 4–6 different animals. Quin, quinolinic acid. *$P < 0.05$, significantly different from control values by Student’s $t$-test. The levels of L-kynurenine and Quin concentrations in control and renal-insufficient rats were, respectively, as follows: serum L-kynurenine ($\mu$M), 1.21 ± 0.20 and 4.30 ± 0.33; cerebrospinal fluid (CSF) L-kynurenine (nM), 32 ± 11 and 156 ± 61; serum Quin (nM), 269 ± 88 and 1,160 ± 200; CSF Quin (nM), 30 ± 10 and 164 ± 49. The levels of clinical parameters in control and renal-insufficient rats were, respectively, as follows: serum creatinine (mg/dl), 0.67 ± 0.05 and 2.4 ± 0.2; serum urea nitrogen (mg/dl), 17 ± 1.6 and 84.8 ± 5.2.
DISCUSSION

This study investigated the kynurenine pathway metabolism in human patients with renal insufficiency. We used an animal model to define mechanisms that may be involved with changes that were observed. Our results clearly demonstrate that renal insufficiency is associated in the rat model with reductions in total L-tryptophan levels in the blood and increases in L-kynurenine and Quin levels in the blood and brain. The liver enzyme measurements in the rat model demonstrated that TDO activity was increased in proportion to blood urea nitrogen and creatinine levels, but the activities of kynureninase, 3-HAD, and ACMSDase were significantly decreased. In addition, although renal 24-h clearance in L-kynurenine and Quin was slightly decreased, total urinary excretion of L-kynurenine and Quin was increased. Therefore, the accumulation of serum L-kynurenine and Quin in this model was not mainly related to a decrease of renal excretion but to a decrease in L-kynurenine and Quin degradation and/or combined with an increase in production.

All samples of serum L-tryptophan levels were significantly decreased in renal-insufficient patients before hemodialysis, in comparison with healthy subjects, whereas serum L-kynurenine and Quin levels were significantly increased. In contrast, serum L-kynurenine and Quin in posthemodialysis had significantly decreased when compared with values in prehemodialysis, although total L-tryptophan concentration did not change. As shown in Fig. 2, posthemodialysis levels of serum L-kynurenine and Quin were significantly decreased by ~30 and 75%, respectively, compared with prehemodialysis values. Even though the reason for the differences in the degree of reduction is unknown at present, it is speculated to be due to the protein-binding capacity and washout effect by hemodialysis. Unlike other amino acids, plasma L-tryptophan exists in equilibrium between a free and albumin-bound pool, and L-kynurenine is highly associated with macromolecular species in blood (17). It is also possible that the differences in reduction between L-kynurenine and Quin may be related to the differences of distribution volume and/or kinetic behavior in the body.

Because tissues and CSF samples from renal-insufficient patients are not available in this study, the rat renal-insufficient model was used to clarify possible mechanisms for elevations of L-kynurenine and Quin concentrations in patients with renal insufficiency. In a rat experimental renal-insufficient model, serum L-tryptophan levels were significantly decreased by 22% in only severe cases of renal-insufficient subjects. The increase of serum L-kynurenine levels and reduction of serum L-tryptophan concentrations in rats with severe renal insufficiency are consistent with the induction of TDO and reduction in kynureninase activity in the liver. Because dietary L-tryptophan intake was not regulated or quantified in the present study, we could not exclude the possibility that part of the reductions in serum L-tryptophan concentrations was diet dependent. However, reduced L-tryptophan intake would have been expected to decrease, not increase, L-kynurenine concentrations.

Metabolism of L-tryptophan through L-kynurenine was found to be influenced by TDO activity in liver and indoleamine 2,3-dioxygenase in extrahepatic tissues (2, 29). Hepatic TDO activity is a major determinant of L-tryptophan flux through the kynurenine pathway and L-tryptophan transport into the liver under normal...
levels were consistently lower than regional brain determined, particularly as the magnitude of the indolites in the central nervous system remains to be increased in several tissues and cell types in response to immune stimulation (14, 18, 30), no changes in indoleamine 2,3-dioxygenase activity in lung and brain were observed in the renal-insufficient rats. The mechanisms responsible for the increased activity of TDO include the induction by increased levels of circulating glucagon and/or glucocorticoids (22, 23). As reported previously, concentrations of blood glucagon were elevated in the renal-insufficient rats (Table 2). Because the kidney is a major site of glucagon metabolism, and binding sites for glucagon exist in the liver, these hormone levels may increase in conditions of renal insufficiency (6). It is possible, therefore, that blood glucagon levels may induce TDO activity in renal-insufficient rats. Cortisol levels were slightly increased, although this did not reach statistical significance. The major pathway of L-kynurenine metabolism is by way of hydroxylation followed by cleavage catalyzed by kynureninase, a pyridoxal phosphate (vitamin B6)-dependent enzyme. It is known that rat renal failure results in marked decreases in vitamin B6 content, probably due to the impairment of vitamin B6 absorption (1). Therefore, a significant reduction of the activity of liver kynureninase activities and increased L-kynurenine concentrations after renal insufficiency may be attributable in part to vitamin B6 deficiency. The results of rat experimental renal insufficiency also demonstrate elevated levels of CSF and brain L-kynurenine. Although exact mechanisms of increased brain L-kynurenine levels after renal insufficiency are unknown at present, L-kynurenine may enter the brain from the blood with the increase in L-kynurenine levels (12). Indeed, CSF L-kynurenine levels were consistently lower than regional brain L-kynurenine concentrations. Furthermore, activity of brain indoleamine 2,3-dioxygenase, the enzyme required for synthesizing L-kynurenine from L-tryptophan, was not detectable in either control or experimental renal insufficiency.

The results of experimental renal insufficiency demonstrated elevated levels of serum, CSF, and brain Quin. Quin is a neuroexcitatory, neurotoxic metabolite of L-tryptophan, acting as an agonist of NMDA-type excitatory amino acid receptors, and causes seizures and nerve cell death in large quantities (26, 34). Neurological dysfunction in patients with chronic renal insufficiency have been reported, but the mechanisms are complicated (4, 5, 20). This study demonstrated that increases of serum Quin levels in patients with chronic renal insufficiency were similar to those observed in experimental rats (Fig. 2). However, the pathological and functional significance of the increases in Quin and other kynurenine pathway metabolites in the central nervous system remains to be determined, particularly as the magnitude of the increases was relatively small. If the increased CSF Quin and other kynurenine pathway metabolites account for a part of neurological dysfunction found in renal-insufficient patients, the reduction of these metabolites in serum by hemodialysis may be beneficial.

Under normal circumstances, most L-tryptophan is metabolized to enter the glutamate pathway. It may, however, enter the NAD pathway when ACMSDase activity is low (see Fig. 1 and Ref. 24). This study clearly demonstrates that administration of a strong inhibitor of ACMSDase, pyrazinamide, markedly increased serum Quin and slightly elevated CSF Quin concentrations (Fig. 4). Therefore, changes in body ACMSDase activities in response to renal insufficiency are important factors for the determination of serum Quin concentrations. In addition, although renal 24-h clearance in Quin was slightly decreased, total urinary excretion of Quin was increased (Table 5). Thus changes in concentration are mainly related to metabolism rather than to attenuated excretion. In serum, L-kynurenine and other kynurenine pathway metabolites such as 3-hydroxykynurenine or 3-hydroxyanthranilate would be expected to increase in conditions of renal insufficiency and may transverse the blood-brain barrier and be converted to Quin (8). The accumulation of brain Quin in renal-insufficient rats may be derived from serum Quin and/or Quin precursors. Furthermore, the possibility that a part of the increased serum Quin is originated from Quin in blood is not excluded.

In conclusion, acceleration of peripheral kynurenine pathway metabolism occurs in rats with renal insufficiency and runs parallel with the severity of the case. Increased serum L-kynurenine concentrations reflect mainly increased TDO and decreased kynureninase activity in the liver. Increased serum Quin concentrations reflect the decreased ACMSDase activity in the body. We hypothesize that the accumulation of L-kynurenine in the CNS is due to the entry of increased serum L-kynurenine, and the accumulation of Quin may be due to serum-derived Quin and/or Quin precursors.

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REFERENCES

KYNURENINE PATHWAY METABOLISM AND RENAL INSUFFICIENCY


