Deranged Tyrosine Metabolism in Cirrhosis

J. TIMOTHY FULENWIDER, M.D., a BERNARD M. NORDLINGER, M.D., a
BAJHAT A. FARAJ, Ph.D., b GEORGE L. IVEY, B.S., c
AND DANIEL RUDMAN, M.D. d

aResearch Fellow in Portal Hypertension, Department of Surgery; bAssociate Professor, Department of Radiology; cResearch Assistant; Second-year medical student; dProfessor of Medicine and Surgery: Director, Clinical Research Facility; Emory University School of Medicine, Atlanta, Georgia

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In normal individuals, the main route for tyrosine degradation is the hepatic pathway tyrosine → 4-hydroxyphenylpyruvic acid → homogentisic acid → CO₂. Quantitatively minor pathways, in large part extrahepatic, are: tyrosine → tyramine → octopamine and tyrosine → dopa → catecholamines.

In cirrhosis, the main hepatic pathway is blocked to varying degrees at the first three stages. This appears to be due to lack of activity of the enzymes tyrosine transaminase, PHPA oxidase, and HGA oxidase, the first step being rate limiting. Hypertyrosinemia and tyrosine intolerance result.

With the main hepatic pathway partially blocked, an abnormally large amount of tyrosine passes into the normally minor extrahepatic pathway leading to the false neurotransmitters tyramine and octopamine. Overproduction of these amines ensues and they accumulate in the body fluid.

The false neurotransmitters can displace catecholamines from their storage sites in the peripheral and central nervous system, and thereby disrupt adrenergic processes in arterioles, kidneys, and brain. Their accumulation in cirrhotic patients may play a role in the pathogenesis of hepatic encephalopathy, hepatorenal syndrome, and hyperdynamic circulation.

HISTORY

The earliest recorded observation of deranged tyrosine metabolism in liver disease was Rokitansky[1], who in 1849 noted crystals of tyrosine in the liver of patients with acute hepatic necrosis. Five years later Frerichs[2], described tyrosine crystals in the urine of patients with acute yellow atrophy. In 1924, the indispensable role of the liver in amino acid catabolism was documented by Bollman, Mann, and Magath[3] when they showed that heptectomy abolished the ability of dogs to synthesize urea. In 1943, Bernhart and Schneider[4], using a colorimetric technique, demonstrated fasting hypertyrosinemia in patients with liver disease and described tyrosine intolerance following an oral challenge of this amino acid.

The automated ion-exchange amino acid analyzer, developed in the 1950s, stimulated interest in plasma amino acid profiles in various disease states. Using this
improved technique Iber [5], in 1957, measured individual amino acid levels in two normal subjects and in seven cirrhotics, five of whom had hepatic encephalopathy. The most characteristic features of the "plasma aminogram" in the cirrhotic group were elevations of both methionine and tyrosine disproportionate to the rise in total plasma amino acids. This confirmed the research done two years previously by Wu, Bollman, and Butt, who used paper chromatography to measure amino acid levels in patients with hepatic coma [6]. Iber also found that the level of plasma amino acids rose with increasing liver decompensation but that the level of total plasma amino acids was not consistently elevated in hepatic coma. The diagnostic significance of hypertyrosinemia in liver disease was first emphasized by Cachin, Durlach, and Blass [7], who stated that an elevated concentration of plasma tyrosine was the earliest plasma derangement of liver disease.

In 1967, utilizing a specific fluorometric method, Levine and Conn [8] further investigated tyrosine metabolism in patients with cirrhosis or hepatitis and in normal controls. Fasting tyrosine levels tended to be slightly increased in patients with hepatitis and biliary obstruction and markedly increased in patients with cirrhosis. Following an oral load of tyrosine (50 mg/Kg body weight), patients with cirrhosis demonstrated larger than normal increments in tyrosine levels and delayed return to fasting levels when compared to normal controls. In patients with liver disease (particularly cirrhosis) there was marked impairment in tyrosine synthesis following an oral load of 100 mg/Kg body weight of phenylalanine.

After 1967, with the exception of scattered reports, no new chapters were added to the story of abnormal tyrosine metabolism in liver disease, and hepatologists' attention was diverted toward other aromatic compounds incriminated in producing the neurologic complications of cirrhosis. The failure of the hepatologists to pursue the mechanism for the tyrosinemia is surprising, because (as is reviewed below), pediatricians during the period 1930–1950 had been successful in delineating the enzyme defects responsible for hereditary hypertyrosinemia and related hereditary metabolic disorders.

A new trail of research on aromatic amino acids in cirrhosis emerged when Fischer and Baldessarini [9] proposed that false neurotransmitters derived from tyrosine (tyramine and octopamine) were the mechanism responsible for the altered physiology of the central nervous, cardiovascular, and renal systems in hepatic failure. They theorized that aromatic amines are continually produced by the action of bacterial decarboxylases upon dietary phenylalanine and tyrosine. In normal individuals, these bioactive amines are efficiently cleared from the portal blood by hepatic monoamine oxidases. However, in cirrhotics with impaired hepatocellular function and porto-systemic shunting, Fischer proposed that these amines enter the systemic circulation and "flood" the peripheral and central nervous system. Tyramine and octopamine are indirect sympathomimetic amines whose actions presumably derive from their ability to release norepinephrine; their chronic accumulation in cirrhosis could deplete norepinephrine stores and consequently account for the lowered peripheral arteriolar resistance, peripheral arteriovenous shunts with a secondary hyperdynamic circulation, and impaired renal cortical perfusion [10] seen in cirrhotic patients. In the central nervous system, such replacement of normal neurotransmitters could cause the altered mental state and extrapyramidal features of hepatic disease [11]. In support of this false neurotransmitter hypothesis, Fischer and coworkers described significant elevations of plasma and urinary octopamine in cirrhotics with hepatic encephalopathy, with the degree of octopaminuria correlating with the depth of encephalopathy. Since this original report, Lam et al., in 1973 [12], and Manghani
et al., in 1975 [13], also were able to demonstrate marked accumulation of octopamine in plasma and urine of encephalopathic cirrhotics. In 1976, Faraj and coworkers [14–16] evaluated the role of plasma tyramine (the metabolic precursor of octopamine). The tyramine level in cirrhotic patients with encephalopathy was significantly higher than in normal subjects or in non-encephalopathic cirrhotics. Plasma tyramine was directly correlated with plasma tyrosine. Increasing dietary protein from 40 to 80 grams/day increased fasting tyramine concentration 30 to 70 percent within three days in both encephalopathic and non-encephalopathic cirrhotics.

To summarize, a disturbance in tyrosine metabolism in cirrhosis has been recognized for over a century, and there is recent evidence to suggest that deranged tyrosine metabolism may cause the cardiovascular and neurological complications of liver disease. Recent investigation has focused on the false neurotransmitters, tyramine and octopamine, while study of the metabolism of tyrosine itself has been interrupted prematurely.

The purpose of this article is twofold: to review the metabolic pathways which link tyrosine, tyramine, and octopamine in health and disease; and to describe recent studies by the authors on the metabolism of these compounds in normals and cirrhotics. Our findings lead to a hypothesis explaining the simultaneous accumulation of tyrosine, tyramine, and octopamine in the plasma of cirrhotic patients.

NORMAL TYROSINE METABOLISM

Tyrosine is present in all proteins and is required throughout life for the continuing synthesis of these macromolecules. Tyrosine can be synthesized from phenylalanine, so that a diet furnishing the minimum daily requirement (1 gm/day) of the latter amino acid can be devoid of tyrosine without ill effect. The presence of tyrosine in the diet, however, reduces the daily requirement of phenylalanine. In practice, the American diet contains both amino acids in considerable excess over the minimum daily requirements, viz. about 3–5 grams of tyrosine and 4–5 grams of phenylalanine daily. Efficient small intestinal absorption and renal tubular conservation of tyrosine preserve the large tyrosine pool from which tissue proteins, catecholamines, melanin, and thyroid hormones are synthesized.

The excess of tyrosine in the diet over that needed for biosynthetic processes causes no problems in the normal individual, because of the efficiency of the pathways for tyrosine degradation. There are three major pathway for tyrosine metabolism as illustrated in Fig. 1:

Pathway 1: The main hepatic oxidative pathway for tyrosine degradation, tyr—PHPA—HGA—CO₂ (tyr, PHPA, and HGA signify tyrosine, 4-hydroxyphenylpyruvic acid, and homogentisic acid, respectively).

Pathway 2: The quantitatively minor extrahepatic decarboxylation pathway leading to the false neurotransmitters tyramine and octopamine.

Pathway 3: The quantitatively minor extrahepatic pathway leading to the catecholamines dopamine and norepinephrine. Normally, > 98 percent of tyrosine is degraded via the main intrahepatic oxidative pathway.

After tyrosine enters the hepatocyte, the first step is a reversible transamination reaction that yields PHPA and is catalyzed by tyrosine aminotransferase, an enzyme concentrated in the cytosol and mitochondria of mammalian liver and having a rapid turnover rate of 3–4 hours. The co-substrate for the aminotransferase is α-ketoglutarate; pyridoxal phosphate is required for optimal activity. The transamination reaction is normally rate-limiting for tyrosine oxidase, and although it is reversible, the equilibrium favors keto-acid formation [17].
FIG. 1. Pathways of tyrosine metabolism “PH” denotes phenylalanine hydroxylase; “TH”, tyrosine hydroxylase; “DD,” dopa decarboxylase; “TT,” tyrosine transaminase; “PO,” 4-hydroxyphenylpyruvic acid oxidase; “HO,” homogentisic acid oxidase; “DBH,” dopamineβ-hydroxylase; and “MAO,” monoamine oxidase.

The second intrahepatic reaction, oxidation of PHPA to HGA, is catalyzed by a copper-containing enzyme, PHPA oxidase. HGA is formed by a complex series of reactions involving hydroxylation of the aromatic ring of PHPA, migration of the pyruvyl side-chain, and decarboxylation to an acetyl side chain.

The final step in the catabolic pathway, oxidation of HGA to 4-maleylacetoacetic acid, is catalyzed by HGA oxidase, an Fe (II) enzyme found principally in the liver and requiring reduced glutathione. Both of the aforementioned dioxygenases require ascorbic acid for maximal activity in vivo. Fumarylacetoacetate is then formed by isomerization of the maleyl-analog, following which hydrolysis yields fumaric and acetoacetic acids. The latter product receives a coenzyme A moiety to produce acetoacetyl-CoA, the process being catalyzed by 3-ketoacid CoA transferase. Acetoacetyl CoA is oxidized to acetyl-CoA, which enters the Krebs tricarboxylic acid cycle to produce high energy phosphates and carbon dioxide.

Pathway 2 for tyrosine metabolism is responsible for the extrahepatic production of tyramine and octopamine. Normally about 1–2 percent of total tyrosine metabolic flux proceeds through this route. The production of tyramine from tyrosine involves a decarboxylation reaction by aromatic-L-amino acid decarboxylase which is present in liver, kidney, intestine, brain, adrenal, and lung. David et al. [18,19] have shown that endogenous production of tyramine from tyrosine via decarboxylation becomes a major pathway for the catabolism of tyrosine when the dietary intake of this amino acid in mice is increased to three times the minimal daily requirement.

The tyramine formed is then oxidized to 4-hydroxyphenylacetic acid by monooamine oxidase (MAO), primarily in the liver. MAO requires NAD as cofactor and exhibits some substrate inhibition. While MAO is most highly concentrated in the liver, it is also present in lesser amounts in brain, intestine, kidney, and platelet. A minor by-product of tyramine metabolism is octopamine, formation of which is
catalyzed by the action of dopamine $\beta$-hydroxylase. It is normally found in adrenergic nerve terminals at about 5 percent of the normal synaptic vesicle concentration of norepinephrine. Subsequent degradation of octopamine to 4-hydroxymandelic acid by MAO occurs principally in the liver, but also to a minor degree in the brain and heart. Urinary 4-hydroxymandelate is octopamine's major catabolic metabolite. Tyramine normally may also be excreted by the kidneys [20]; healthy adults excrete approximately 0.5 to 1 mg per day.

Pathway 3 for tyrosine metabolism leads to the catecholamines, and begins with the formation of dopa from tyrosine by the action of tyrosine hydroxylase which is present in the adrenal gland, brain, heart, and spleen. The hydroxylase requires tetrahydropterin and possibly Fe (III) as cofactors, exhibits substrate inhibition control, and is thought to be the rate-limiting step in catecholamine synthesis. L-dopa is then decarboxylated to dopamine by the enzyme dopa decarboxylase, located in kidney, liver, intestine, brain, and lung, and requiring pyridoxal phosphate as a cofactor. $\beta$-Hydroxylation of dopamine by the enzyme dopamine-$\beta$-hydroxylase leads to the formation of norepinephrine, the major neurotransmitter in the peripheral adrenergic nervous system and an important central nervous system (CNS) neurotransmitter. This enzymatic reaction occurs in the adrenal gland, heart, sympathetic ganglia, and salivary gland. From norepinephrine, epinephrine is synthesized principally in the adrenal medulla, heart, and brain by phenylethanolamine-N-methyltransferase. Catecholamines are metabolized in the liver and in the effector cells by two enzymes catechol-O-methyl transferase and monoamine oxidase, with production of acetylated and O-methylated products (3-O-methyldopamine, normetanephrine, metanephrine, homovanillnic acid and vanillylmethacetic acid).

Tyramine and other aromatic amines can also be formed in the gastrointestinal tract by the action of bacterial decarboxylases on tyrosine and other aromatic amino acids. Normally the aromatic amines generated within the colon are cleared from the portal circulation efficiently by hepatic MAO; therefore, systemic bioavailability of these enteric amines is normally negligible. Decarboxylation of amino acids in the intestinal wall is an additional source of aromatic amines [21,22]. Such foods as cheese and red wine have high tyramine concentrations and could contribute substantially to the metabolic burden of these amines, particularly when MAO is inhibited by drugs or disease [23].

**INBORN ERRORS OF PHENYLALANINE-TYROSINE METABOLISM**

During 1932–1953, investigators were successful in identifying several hereditary blocks in the phenylalanine-tyrosine pathways. Their strategy was similar for each hereditary syndrome: (1) Identify the metabolites which had accumulated in plasma and urine; these must have been produced proximal to the block. (2) Perform oral “loading tests” of each metabolic intermediate in the pathway under study. (3) Confirm the conclusion about the defective enzyme developed from (1) and (2) by assaying appropriate enzymes in tissue samples.

Using the above techniques, Grace Medes [24] in 1932, investigated a 49-year-old man with “hereditary tyrosinosis” who was excreting gram quantities of PHPA. Her demonstration, that the metabolic defect in this patient was a deficiency of PHPA oxidase, served as a model for the study of other inborn errors of tyrosine metabolism.

Phenylketonuria is a syndrome characterized by mental retardation, deficient pigmentation, eczema, seizures, and other neurological symptoms. During 1938–
1960, Jervis [25] showed the cause to be a deficiency of phenylalanine hydroy-
ylase, with consequent accumulation of phenylalanine, phenylpyruvic acid, and other
phenylalanine metabolites.

Alkaptonuria was among the first hereditary metabolic diseases to be recognized.
This disorder is characterized by degenerative arthritis in middle age, dark urine, and
bluish discoloration of the cartilaginous portion of the ear and of the sclera.
Homogentisic acid accumulates and is deposited in polymerized form as a dark
pigment in connective tissue (ochronosis). HGA is excreted in the urine in amounts as
great as 1 g/day: oxidation of the urinary HGA leads to the formation of a black
polymer, especially at an alkaline pH. LaDu[26] showed that the disease is caused by
a deficiency of HGA oxidase.

The first description of hereditary tyrosinemia was by Baber in 1956 [27]. The
syndrome comprises renal tubular abnormalities, vomiting, diarrhea, abdominal
enlargement, dyspnea, hemorrhages, edema, ascites, rickets, hepatosplenomegaly,
and occasional mental retardation. The cause is a deficiency of PHPA oxidase.
Biochemical consequences of this deficiency are hypertyrosinemia and abnormally
high urinary excretion of PHPA and its reduction product p-hydroxyphenylacetic
acid.

Thus, inherited disorders of phenylalanine and tyrosine metabolism represent a
spectrum of diseases ranging from minimal clinical symptoms and signs as seen in
alkaptonuria, to life-threatening disorders such as phenylketonuria and hereditary
tyrosinemia. Each disease is characterized by accumulation in plasma and urine of
phenylalanine, tyrosine, or metabolic intermediates in the pathways for degradation
of these amino acids.

ACQUIRED DISORDERS OF TYROSINE METABOLISM IN CIRRHOSIS:
RECENT STUDIES IN THIS LABORATORY

The success of the earlier pediatric investigators in identifying the hereditary blocks
of tyrosine metabolism by means of analyses for metabolic intermediates and by
appropriate loading tests, suggested to us that these same techniques could also be
used to identify the acquired blocks in cirrhosis. We have therefore used these
methods to investigate the main hepatic oxidative pathway (1, in Fig. 1). To
investigate pathway 2, we applied a different technique of metabolic research, which
was borrowed from the clinical pharmacologists. Using the “pharmacokinetic
method” [28,29,30], we studied the mechanism for the accumulation of tyramine by
injecting a tracer dose of the labeled amine and measuring the rate of its turnover in
normal subjects and cirrhotics [31].

The results can be summarized as follows.

(a) Pathway I: Eighteen cirrhotic patients were studied [32], 13 alcohol-induced
and five post-necrotic. All had liver biopsies and full clinical and biochemical
evaluation; nine were grade A, five grade B, and four grade C by Child’s classification.
All exhibited fasting tyrosinemia and abnormally marked and prolonged
elevation of plasma tyrosine levels after an oral dose of 3 grams of tyrosine
(“impaired tyrosine tolerance”). Two intermediates in the pathway, PHPA and
HGA, were measured in the urine in the basal state, after the oral load of tyrosine and
after an oral load of 3 grams of PHPA or HGA. In the basal state, and after the load
of tyrosine, the urinary excretions of PHPA and HGA were normal. After an oral
load of PHPA or HGA, however, the cirrhotics excreted abnormally large amounts
of PHPA or of HGA, respectively. The severity of the intolerances of tyrosine, of
PHPA, and of HGA were not correlated with the rate of portal blood flow and degree of portal shunting, which were evaluated by visceral angiography (venous phase of superior mesenteric artery angiogram). The lack of correlation between the metabolic and vascular abnormalities suggested that the metabolic blocks in pathway 1 were mainly caused by enzyme deficiencies rather than by subnormal portal blood flow.

These findings led to the conclusion that cirrhosis causes loss of activity of tyrosine aminotransferase, PHPA oxidase, and HGA oxidase, the first three enzymes in pathway 1, but that the rate-limiting enzyme is the aminotransferase. This formulation explains the intolerances of tyrosine, PHPA, and HGA, and the normal urinary excretion of the latter two intermediates in the basal state and after the tyrosine load.

(b) Pathway 2: Earlier work here [14] and elsewhere [10] had demonstrated that cirrhosis is accompanied by appreciable accumulations of tyramine and octopamine, decarboxylated products of tyrosine. These accumulations could result either from overproduction of tyrosine, consequent to the obstruction in pathway 1 demonstrated above, or from retarded degradation, consequent to loss of hepatic MAO [33] and lowered hepatic blood flow.

To distinguish between these two possible mechanisms, we evaluated the production rate and metabolic clearance rate of tyramine as well as other kinetic parameters following the single intravenous administration of \(^3\)H-tyramine to a group of cirrhotics and control subjects. The data showed that the plasma clearance of tyramine in hypertyraminemic cirrhotics was normal (ave. 12 ± 1.88 L/min), but the rate of production of tyramine was 2 to 10 × elevated (ave. 33 µg/minutes). Thus, the hypertyraminemia was caused by overproduction from tyrosine, not by loss of capacity to degrade the amine by MAO. As expected from this formulation, the degree of hypertyraminemia, the magnitude of overproduction of tyramine, and the severity of the tyrosine intolerance, were all correlated with each other in the cirrhotic group studied.

HYPOTHESIS

The data are all consistent with the following scheme. Cirrhotic patients are blocked at three enzymatic steps in pathway 1: tyrosine aminotransferase, PHPA oxidase, and HGA oxidase. The rate-limiting obstruction is at the aminotransferase reaction. As tyrosine accumulates because of this block (hypertyrosinemia), it flows at an abnormally high rate into pathway 2, with consequent overproduction of tyramine and octopamine and accumulation of these amines in plasma, tissues, and urine.

CLINICAL IMPLICATIONS

Fischer and coworkers have suggested [34] that the accumulation of tyramine and octopamine may contribute to the pathogenesis of 3 common complications of cirrhosis: hepatic encephalopathy, hyperdynamic circulation, and hepatorenal syndrome. These noncatecholic phenylethylamines are believed to utilize the same uptake system as norepinephrine in entering the adrenergic terminals, and therefore cause a considerable depletion of tissue norepinephrine when accumulated in significant quantities. As a result of this disruption of both peripheral and central adrenergic mechanisms, vasodilatation may occur and this may contribute to the development of low peripheral resistance, high cardiac output, and renal failure in cirrhotics. Furthermore, displacement of dopamine and norepinephrine in the CNS.
by tyramine and octopamine could affect brain function and consequently lead to the occurrence of hepatic encephalopathy. These amines cross the blood-brain barrier only slowly; but tyrosine enters the CNS by a specific transport system, and the enzymes of pathway 2, present in brain, are capable of producing tyramine and octopamine locally.

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