ORIGINAL ARTICLE

Serotonin and melatonin secretion and metabolism in patients with liver cirrhosis

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KEY WORDS

liver cirrhosis, melatonin, serotonin, 5-hydroxyindoleacetic acid, 6-sulfatoxymelatonin

ABSTRACT

INTRODUCTION Hepatic encephalopathy is one of the symptoms of liver failure. The exact causes of encephalopathy are complex and still unclear. Apart from elevated blood ammonia levels, the role of numerous other factors is being considered.

OBJECTIVES The aim of the study was to determine the serum level of serotonin and melatonin and the urinary excretion of their metabolites (5-hydroxyindoleacetic acid [5-HIAA] and 6-sulfatoxymelatonin [6-HMS]) in patients with various stages of liver cirrhosis.

PATIENTS AND METHODS The study comprised 75 patients with alcohol-induced liver cirrhosis and 25 healthy subjects (control group). Based on the Child-Pugh classification, 3 groups of 25 patients each were distinguished – group A, B, and C with grade A, B, and C of liver failure, respectively. Blood samples were drawn at fasting at 9 a.m., and 24-hour urine collection was performed. Immunoenzymatic assays were used to determine serum melatonin and serotonin levels as well as urine 5-HIAA and 6-HMS concentrations.

RESULTS Serum serotonin levels were 159.8 ±23.1 ng/ml in controls, 179.3 ±21.1 ng/ml in group A ($P > 0.05$), 143.2 ±22.8 ng/ml in group B ($P > 0.05$), and 114.5 ±37.6 ng/ml in group C ($P < 0.01$). Serum melatonin levels were 10.6 ±1.7 in controls, 31.2 ±9.8 pg/ml in group A ($P < 0.01$), 49.8 ±12.2 pg/ml in group B ($P < 0.001$), and 94.8 ±22.6 pg/ml in group C ($P < 0.001$). Urinary 5-HIAA excretion was 5.9 ±2.1 mg/24 h in controls, 5.9 ±1.9 mg/24 h in group A ($P > 0.05$), 4.8 ±1.2 mg/24 h in group B ($P > 0.05$), and 4.6 ±1.4 mg/24 h in group C ($P < 0.05$). Urinary 6-HMS excretion was 26.6 ±15.1 µg/24 h in controls, 23.2 ±7.9 µg/24 h in group A ($P > 0.05$), 18.3 ±10.6 µg/24 h in group B ($P > 0.05$), and 6.5 ±3.6 µg/24 h in group C ($P < 0.001$).

CONCLUSION Disturbances in serotonin and melatonin homeostasis observed in patients with liver cirrhosis may be associated with advanced encopaholopathy.

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INTRODUCTION Serotonin is formed in the body from exogenous L-tryptophan. The process of serotonin synthesis occurs in the gastrointestinal (GI) tract, central and peripheral nervous system, and immune system cells.[1,2] The GI tract is the largest source of serotonin. Approximately 90% of total serotonin is found there and is synthesized mainly in the enterochromaffin cells.[3]

Serotonin, after finding its way to the extracellular space, is captured by reuptake transporters, mainly by serotonin reuptake transporter (SERT). SERT is widely expressed in enterocytes, neurons of the central and peripheral nervous system, and in blood platelets,[4,5] where serotonin is metabolized and its main metabolites, 5-hydroxyindoleacetic acid (5-HIAA) is excreted in urine.[6] Basic secretion of serotonin by the enterochromaffin cells in the GI tract is high and increases as a result of pH changes, osmolarity of the intestinal contents, intraintestinal pressure, toxins, some drugs, and β-adrenergic and muscarinic stimulation.

Pinealocytes and GI enterochromaffin cells are a rich source of melatonin. The pineal gland

secretes this hormone in the circadian rhythm, mainly regulated by light stimuli.[7,8] It is released from the GI tract, under the effect of various stimuli and plays a significant enteroprotective role in the paracrine mechanism.[9,10] Then, it is metabolized (in insignificant quantity) in enterocytes via enzymatic fraction CYP1B1.[11] Its main part enters the liver through a portal system where about 90% of circulating melatonin is deactivated after the first pass.[12] Melatonin is metabolized by cytochrome P-450 enzymes (CYP1A1, CYP1A2) in hepatocytes to its main metabolites: 6-sulfatoxymelatonin (6-HMS) and 6-hydroxymelatonin glucuronide, which are excreted in urine.[13,14] Possibly, part of melatonin is excreted in its unchanged form also to the bile because melatonin concentration in this systemic fluid is also high.[15,16]

Before biodegradation, melatonin fulfils an extremely important biological role. Intensive metabolic processes occur constantly in hepatocyte mitochondria, resulting in detoxification of the body. Simultaneously, increased release of reactive oxygen species that can damage liver cells is observed in these processes. Melatonin, demonstrating mainly antioxidant properties, protects them against such negative effects.[17-19]

Serotonin and melatonin homeostasis can change in various pathological conditions. Liver cirrhosis can be one of them, particularly during hepatic failure and portal hypertension. In these patients, secondary changes in the GI tract occur, known as secondary enteropathy. In the altered intestinal wall, disturbances both in serotonin synthesis and metabolism are observed. Serotonin leakage to systemic circulation cannot be excluded. It could be manifested by anxiety, sleep disorders, and other emotional disturbances.[20] Then, the liver should play the role of a filter, where serotonin is catabolized. This mechanism fails in the case of liver diseases. In experimental studies on rats with toxic hepatocellular damage, a marked increase of serotonin and 5-HIAA concentrations was observed in brain structures.[21] However, it is not clear whether these products originated in the brain or in the GI tract, because the applied toxic agent (thioacetamide), such as cytostatics, can induce serotonin synthesis in the enterochromaffin cells. Regardless of the source of serotonin, the increase of its level can cause symptoms from the central nervous system (CNS) similar to those occurring in patients with hepatic encephalopathy.

Such changes could be related to melatonin because impaired liver is not able to metabolize its whole pool originating from the GI tract. This was confirmed by numerous studies showing changes in blood melatonin levels in patients with chronic liver diseases.[22,23]

Moreover, in liver cirrhosis, the circadian rhythm of pineal melatonin secretion is disturbed and its concentration in blood peaks in the morning hours.[24,25] There have been numerous attempts to explain this phenomenon. It has been suggested that metabolic disorders associated with liver failure might account for those morning peaks of melatonin.[26] Zee et al.[27] and Coy et al.[28] observed such changes in the rhythm of melatonin secretion in rats after creation of portal-systemic anastomosis. In turn, Finn et al.[29] observed, under similar experimental conditions, that after oral administration of neomycin, the normal rhythm of melatonin secretion was restored. A conclusion was drawn from these studies that higher blood ammonia concentrations has a toxic effect on brain structures, including the pineal gland, and that it changes the rhythm of melatonin secretion.[30,31]

All the above changes could have a significant impact on the clinical course of liver cirrhosis.

The aim of our study was to determine serum serotonin and melatonin levels and the urinary excretion of their metabolites (5-HIAA, 6-HMS) in patients in various stages of liver cirrhosis.

PATIENTS AND METHODS

Patients The study comprised 75 patients (aged from 29 to 63 years) with alcohol-induced liver cirrhosis grade A (group A; n = 25), grade B (group B; n = 25), and grade C (group C; n = 25) of the Child-Pugh classification.[32] The control group comprised 25 healthy subjects aged from 26 to 54 years. A written consent was obtained from all the examined patients and the Ethical Committee of the Medical University of Lodz, Łódź, Poland, approved the study protocol (RNN/272/05/KB). All patients had abused alcohol for the period of 6 to 21 years. The diagnosis was based on environmental factors, clinical examination, diagnostic imaging (ultrasonography, panendoscopy, computed tomography), and laboratory investigations. At the same time, all patients were subjected to psychological and psychometric testing, e.g., the number connection test (NCT-A, NCT-B) and line tracing test to determine the severity of encephalopathy according to the West Haven criteria.[33,34]

Methods The following routine biochemical tests were performed several times: blood cell count, bilirubin, alanine transaminase, aspartate transaminase, γ-glutamyltranspeptidase, alkaline phosphatase, glucose, cholesterol, urea, ammonia, creatinine, glomerular filtration rate, prothrombin, albumins, globulins as well as the surface antigen of the hepatitis B virus and antihepatitis C virus. Blood samples were drawn at 9 a.m., and 24-hour urine collection was performed. At night, patients remained in rooms with no access to white light. Three days prior to the examination and on the day of the examination, patients remained on the same standard diet, i.e., Nutridrink (Nitrison) 3 × 400 ml (1800 kcal) and 1500 ml of mineral water. Blood was centrifuged and then the serum was stored at –70°C. Serum melatonin and serotonin levels and urine 5-HIAA and 6-HMS concentrations were determined by an immunoenzymatic method (IBL, RE 59 021, RE 59 121, RE 59 131, and RE 59 031 kits; IBL, Germany).

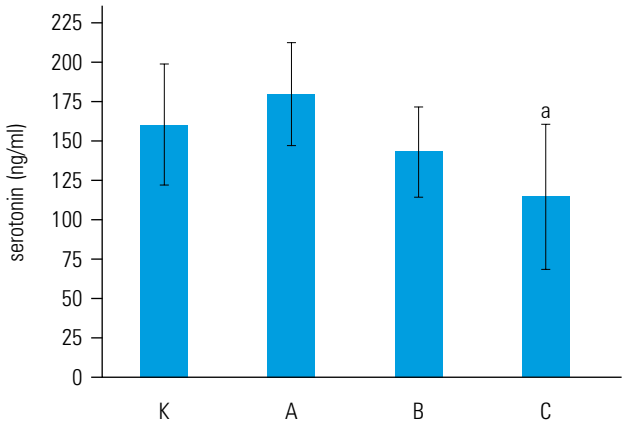

FIGURE 1 Serum serotonin levels in healthy subjects (K) and patients with different grades of hepatic insufficiency (A, B, C – according to the Child-Pugh score); **a** $P < 0.01$

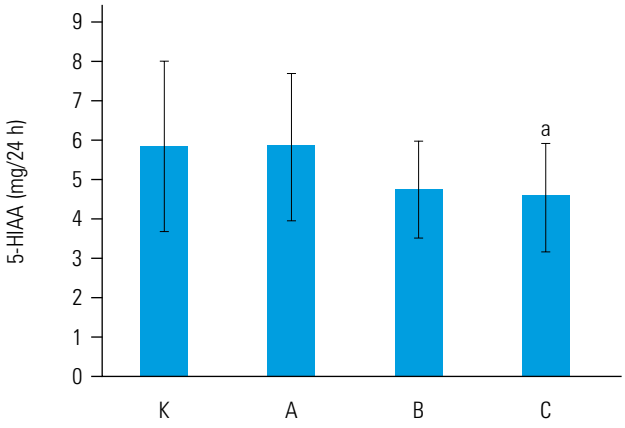

FIGURE 2 Urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion in healthy subjects (K) and patients with different grades of hepatic insufficiency (A, B, C – according to the Child-Pugh score); **a** $P < 0.05$

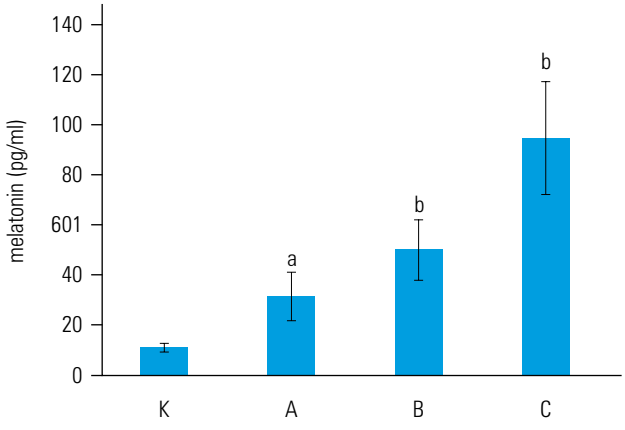

FIGURE 3 Diurnal serum melatonin levels in healthy subjects (K) and patients with different grades of hepatic insufficiency (A, B, C – according to the Child-Pugh score); **a** $P < 0.01$, **b** $P < 0.001$

Statistical analysis The nonparametric Kruskal-Wallis test was used to compare melatonin concentration in a given grade of liver failure and the Mann-Whitney *U* test was applied for paired comparison. The verification of significance of the differences in the results was performed at the level of $P = 0.05$, $P = 0.01$, and $P = 0.001$. The Statistica and the Excel (Microsoft Co.) software were used for statistical analysis.

RESULTS In healthy subjects, the mean serum serotonin level was 159.8 ±23.1 ng/ml (FIGURE 1). In the group of patients with liver cirrhosis, serotonin levels differed depending on the severity of liver failure. The levels were 179.3 ±21.1 ng/ml in group A ($P > 0.05$), 143.2 ±22.8 ng/ml in group B ($P > 0.05$), and 114.5 ±37.6 ng/ml in group C ($P < 0.01$).

The urinary 5-HIAA excretion was 5.9 ±2.1 mg/24 h in the control group, 5.9 ±1.9 mg/24 h in group A ($P > 0.05$), 4.8 ±1.2 mg/24 h in group B ($P > 0.05$), and 4.6 ±1.4 mg/24 h in group C ($P < 0.05$) (FIGURE 2).

In the morning hours, the mean serum melatonin level was 10.6 ±1.7 pg/ml in the control group, 31.2 ±9.8 pg/ml in group A ($P < 0.01$), 49.8 ±12.2 pg/ml in group B ($P < 0.001$), and 94.8 ±22.6 pg/ml in group C ($P < 0.001$) (FIGURE 3).

The urinary 6-HMS excretion was 26.6 ± 15.1 µg/24 h in the control group, 23.2 ±7.9 µg/24 h in group A ($P > 0.05$), 18.3 ±10.6 µg/24 h in group B ($P > 0.05$), and 6.5 ±3.6 µg/24 h in group C ($P < 0.001$) (FIGURE 4).

DISCUSSION The results confirm the findings of other investigators that homeostasis of both serotonin and melatonin is disturbed in patients with liver cirrhosis, but these changes depend on the grade of liver failure. Particularly significant changes occur in patients with advanced liver failure and severe hepatic encephalopathy.

Hepatic encephalopathy is a complex neuropsychiatric syndrome characterized by disturbances in behavior and cognition and by neurological signs.[35] The exact causes of encephalopathy are unknown. Impairment of the liver cells, which cannot detoxify the toxic compounds formed in the body during various biochemical processes, and shunting of blood from the portal to systemic circulation are the main factors in the pathogenesis of this type of encephalopathy. Under these conditions, toxic substances are transported with portal blood to various organs including the brain, where they cause metabolic disorders. Ammonia is most frequently listed among the substances contributing to encephalopathy. It disturbs enzymatic processes of the brain tissue, inhibits acetylocholine and dopamine activity, and intensifies the storage of false neurotransmitters. However, high levels of ammonia in blood are not detected in all patients with encephalopathy, and in these cases other compounds and metabolites may be involved in its pathogenesis. The synthesis of physiological neurotransmitters decreases in the brain tissue in response to those compounds and false neurotransmitters accumulate. This, in turn, leads to such symptoms as tremor or psychoemotional disorders.[36,37] Consciousness impairment is also explained by elevated concentration of many neurotransmitters and

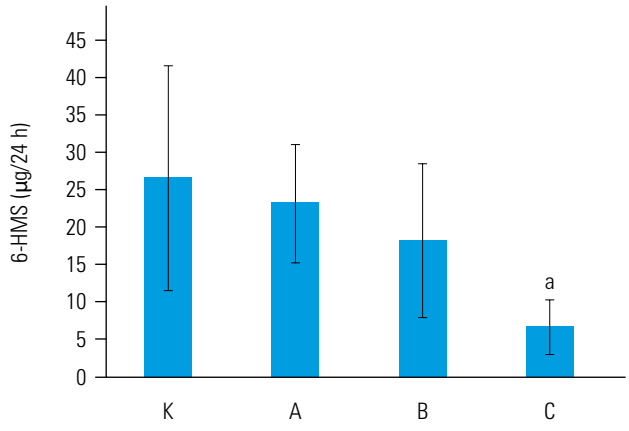

FIGURE 4 Urinary 6-sulfatoximelatonin (6-HMS) excretion in healthy subjects (K) and patients with different degrees of hepatic insufficiency (grades A, B, C – according to the Child-Pugh score); **a** $P < 0.001$

other biologically active compounds in the brain, including serotonin.

Our own studies have shown that serotonin secretion is associated with the grade of liver failure. In the initial stage, its blood levels do not change significantly and they are even higher in patients than in healthy subjects. This may be caused by increased secretory activity or proliferation of the enterochromaffin cells. The weakening of the activity of reuptake protein transporters can also lead to an increase in blood serotonin levels.

In the case of portal enteropathy, the possibility of serotonin leakage through the intestinal wall into the blood stream should be considered. Serotonin can escape from portal vessels into the systemic circulation through shunts, and it can disturb the function of many organs via numerous receptors.[38] In the GI tract, it can release dyspeptic symptoms and may cause disturbances of the intestinal passage. Serotonin induces vasospasms through 5-HT_{1b} and 5-HT_{2a} receptors, which leads to the development of coronary syndromes. Most probably, similar reactions occur in the vessels within other organs (including the liver), which may be harmful and may constitute an additional pathogenic factor contributing to liver failure. Furthermore, through 5-HT_{2a} receptor located in the endothelial cells, serotonin enhances platelet aggregation, which contributes to portal vein thrombosis.[39] It cannot be excluded that serotonin is also the cause of other symptoms occurring in patients with liver failure such as sleep disorders, chronic fatigue, anxiety, or attention disorder.

A different situation is observed in extreme liver failure and severe hepatic encephalopathy. In these cases, decreased blood serotonin levels as well as decreased urinary 5-HIAA excretion have been observed, which suggests diminished secretion of this neurotransmitter in the body. Mood disorders, apathy, and even depression dominate among the symptoms of encephalopathy in this period. According to one of the concepts, serotonin deficit in the CNS is the cause of mood deterioration and depression. This deficit can occur in different states. The hypothesis put forward by Curzon has suggested that elevated levels of glucocorticosteroids, caused by chronic mental or biological stress, activates hepatic pyrolase, which instead of metabolizing tryptophan into serotonin enhances the conversion of tryptophan to kynurenine and leads to serotonin deficiency.[40,41] Such process occurs in many tissues, including those in the CNS.[42,43] As a result, kynurenine pathway metabolites are formed: kynurenic acid has neuroprotective properties, while quinolinic acid exerts neurotoxic effects. Another metabolite, 3-hydroxikynurenine, shows a similar neurotoxic activity by inducing oxygen free radical generation.[44]

It is interesting that low blood serotonin levels were accompanied by elevated levels of melatonin, especially in patients with advanced liver failure. A simultaneous decrease of urinary excretion of 5-HMS indicates its insufficient metabolism in the liver. From a physiological point of view, hypermelatonemia is beneficial because of its hepatoprotective activity.

The results of the above experimental studies had significant practical implications and encouraged to use melatonin for therapeutic purposes.[45,46] Melatonin has a protective effect on the structure and function of the CNS, and its analogues are used in the therapy of depression. However, the level of all hormones in the body should be appropriate. Both, deficiency and excess of hormones could have unfavorable effect on general well-being. The suspicion arises that high melatonin levels that persist for a long time might result in the occurrence of some clinical manifestations such as fatigue or sleep disorders.

The pathogenesis of hepatic encephalopathy is complex but disturbances in serotonin and melatonin homeostasis may alter clinical presentation of liver cirrhosis. Disturbances in serotonin and melatonin homeostasis observed in patients with liver cirrhosis may be associated with advanced encopaholopathy.

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ARTYKUŁ ORYGINALNY

Wydzielanie i metabolizm serotoniny i melatoniny u pacjentów z marskością wątroby

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SŁOWA KLUCZOWE

kwas 5-hydroksyindolooctowy, marskość wątroby, melatonina, serotonina, siarczan 6-hydroksymelatoniny

STRESZCZENIE

WPROWADZENIE Jednym z objawów niewydolności wątroby jest encefalopatia wątrobowa. Dokładne przyczyny encefalopatii są złożone i nadal niejasne. Oprócz zwiększenia stężenia amoniaku we krwi bierze się pod uwagę rolę wielu innych czynników.

CELE Celem pracy była ocena stężenia serotoniny i melatoniny we krwi oraz wydalania ich metabolitów (kwasu 5-hydroksyindolooctowego [5-HIAA] i siarczanu 6-hydroksymelatoniny [6-HMS]) z moczem u osób z różnym stopniem niewydolności wątroby.

PACJENCI I METODY Badania wykonano u 75 chorych z alkoholową marskością wątroby oraz u 25 osób zdrowych (grupa kontrolna). Na podstawie klasyfikacji Childa i Pugha wyodrębniono 3 grupy po 25 chorych – odpowiednio grupy A, B i C ze stopniem A, B i C niewydolności wątroby. Krew do badania pobierano na czczo o godz. 9:00, a mocz zbierano przez 24 h. Serotoninę i melatoninę w surowicy oraz 5-HIAA i 6-HMS w moczu oznaczano metodą immunoenzymatyczną.

WYNIKI Stężenie serotoniny w surowicy wynosiło 159,8 ±23,1 ng/ml w grupie kontrolnej, 179,3 ±21,1 ng/ml w grupie A ($p > 0,05$), 143,2 ±22,8 ng/ml w grupie B ($p > 0,05$) i 114,5 ±37,6 ng/ml w grupie C ($p < 0,01$). Poziom melatoniny wynosił 10,6 ±1,7 pg/ml w grupie kontrolnej, 31,2 ±9,8 pg/ml w grupie A ($p < 0,01$), 49,8 ±12,2 pg/ml w grupie B ($p < 0,001$) i 94,8 ±22,6 pg/ml w grupie C ($p < 0,001$). Wydalanie 5-HIAA z moczem wynosiło 5,9 ±2,1 mg/24 h w grupie kontrolnej, 5,9 ±1,9 mg/24 h w grupie A ($p > 0,05$), 4,8 ±1,2 mg/24 h w grupie B ($p > 0,05$) i 4,6 ±1,4 mg/24 h w grupie C ($p < 0,05$). Wydalanie 6-HMS z moczem wynosiło 26,6 ±15,1 µg/24 h w grupie kontrolnej, 23,2 ±7,9 µg/24 h w grupie A ($p > 0,05$), 18,3 ±10,6 µg/24 h w grupie B ($p > 0,05$) i 6,5 ±3,6 µg/24 h w grupie C ($p < 0,01$).

WNIOSKI Zaburzenia homeostazy serotoniny i melatoniny u osób z marskością wątroby mogą się wiązać z zaawansowaną encefalopatią.

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