CLINICAL STUDY

Serotonin and 5-hydroxyindole-acetic acid

Sebekova K, Spustova V, Opatrny K Jr., Dzurik R

Institute of Preventive and Clinical Medicine, Bratislava, Slovakia, and Dialysis Center, Department of Internal Medicine, Charles University, Plzen, Czech Republic. **sebekova@upkm.sk**

Abstract

Background: **In patients suffering from chronic renal insufficiency (CRI) serotonin (5HT) metabolism is impaired, and plasma 5-hydroxyindoleacetic acid (5HIAA) levels (main metabolite of 5HT) are increased.**
Aim: **In this study we aimed to give a detailed description of peripheral serotonin metabolism in healthy subjects and patients with CRI, and to evaluate the efficacy of hemodialysis in the elimination of cumulated 5HT and 5HIAA.**
Methods: **5HT (platelet rich plasma, platelet poor plasma, urine, HPLC with electrochemical detection) and 5HIAA (plasma, urine, HPCL with electrochemical detection) levels were evaluated in 14 conservatively treated (CT) and 12 hemodialysed (HD) patients with CRI and were compared to those of 60 healthy volunteers (HV).**
Results: **In patients with CRI accumulation of 5HT and 5HIAA in plasma with no changes in platelet 5HT content was revealed. 5HT renal and fractional excretion (FE) was markedly decreased in CRI. FE-5HT was <1 in all investigated subjects, indicating its reabsorption in proximal tubules, or local degradation to 5HIAA. Due to the increased filtration load renal excretion of 5HIAA was not altered in CT patients, however it was decreased in HD patients. The relative participation of glomerular filtration in 5HIAA renal excretion increased in CRI. FE-5HIAA >5 was found in 20 % of HV and 15 % of CT, pointing indirectly to 5HIAA intrarenal production. In CRI FE-5HIAA decreased. HD did not eliminate accumulated 5HT and 5HIAA effectively.**
Conclusion: **Increased levels of 5HT and 5HIAA might exert metabolic effects contributing to the clinically manifested impairments characteristic for uremic syndrome.** ***(Tab. 3, Fig. 3, Ref. 27.)***
Key words: serotonin, 5-hydroxyindoleacetic acid, chronic renal insufficiency, hemodialysis, renal excretion.

It is widely accepted that indole substances act as uremic toxins. Serotonin (5-hydroxytryptamine, 5HT) synthesis represents only minor metabolic route for tryptophan, since not more than 2 % of ingested tryptophan is utilised for synthesis of 5HT (Tyce, 1985). In periphery 5HT is synthesized in enterochromaffin cells of gastrointestinal wall, probably accounting for the majority of 5HT reaching the blood and in proximal tubular cells of the kidney (Sole et al., 1986) (Fig. 1).

As the high free plasma 5HT concentrations might be deleterious, three processes limit any increase of free 5HT in blood. 1) 5HT is taken up rapidly by plateles, stored in dense granules wherefrom it is liberated during platelet aggregation. In platelet 5HT concentration reaches μmol range, and here 5HT is not exposed to the action of A type monooxidase (MAO A) metabolising 5HT into 5-hydroxy-3-indoleacetic acid (5HIAA) (Gillis, 1985). 2) Plasma 5HT binds to transport proteins (Gershon and Tamir, 1985). 3) Free 5HT is rapidly removed from plasma by endothelial cells, or it is enzymatically degraded (Gillis, 1985). Plasma 5HT and 5HIAA concentrations average in nmol range. They are excreted by kidney mainly via organic cation and anion transport systems (OCTS, OATS).

5HT concentrations in plasma are too low to produce measurable cardiovascular effects. However, free 5HT concentration may increase to the point where significant actions might be anticipated. Physiologically 5HT may cause vasoconstriction or vasodilation (Tanner et al., 1991), it activates platelets and induces platelet aggregation (Holmsen, 1985), and it stimulates mitogenesis (Kent et

Institute of Preventive and Clinical Medicine, Bratislava, Slovakia, and Dialysis Center, Department of Internal Medicine, Charles University, Plzen, Czech Republic

Address for correspondence: K. Sebekova, Dept of Pharmacotherapy UPKM, Limbova 14, SK-833 01 Bratislava, Slovakia.
Phone: +421.2.59369431, Fax: +421.2.59369170

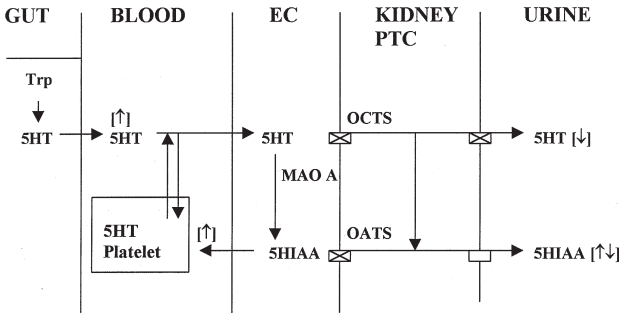

Fig. 1. Scheme of peripheral serotonin metabolism. See text for more details: 5HT — serotonin, 5HIAA — 5-hydroxy-3-indoleacetic acid, EC — endothelial cells, OATS — organic anion transport system, OCTS — organic cation transport system of proximal tubules, MAO A — A type monoaminooxidase, signes in brackets indicate changes in chronic renal insufficiency.

al., 1991). Metabolic effects of accumulated 5HT and 5HIAA are not completely clear by now. 5HT may play a role in ethiopathogenesis of atherosclerosis, aggravation of hypertension, development hypertension caused by erythropoetin (rHuEPO) (Azzadin et al., 1995), and might contribute to development of coagulopathies characteristic for CRI patients. In *in vitro* studies 5HT was shown to exert mitogenic effect with increased activities of cathepsin and an enhanced protein degradation in proximal tubule cell line (LLC-PK1 cells) (Šebeková et al., 1995). In CRI accumulated 5HIAA might play a role in the development of hypercoagulative states or consumptive hypocoagulation (Šebeková et al., 1991), and participate in insulin resistance in advanced renal failure (Šebeková et al., 1996). Enhanced circulating levels of 5HT and 5HIAA could interfere with the binding capacity of the transport proteins and the transport system of organic ions in proximal tubules.

In previous works we demonstrated that 5HT metabolism is impaired, and plasma 5HIAA levels are increased in CRI (Šebeková et al., 1989, 1991). The aim of this study was the concurrent of 5HT and 5HIAA metabolism in order to give a detailed description of this deterioration and to evaluate the efficacy of hemodialysis in the elimination of cumulated 5HT and 5HIAA.

Patients and methods

A study population consisted of three group: 1) healthy controls: 60 healthy volunteers (26 F, 34 M, age range 22—47 years, mean = 34.6 years; 2) 14 CRI patients treated conservatively (CT, 9 F, 5 M, age range 44—74 years, mean = 60.4 years); and 3) 12 patients on maintenance hemodialysis due to end-stage chronic renal failure (HD, 4 F, 8 M, age range 28—58 years, mean = 40.8 years). None of them was anephric.

All subjects were instructed to avoid intake of food interfering with 5HT metabolism one day prior to and during the study. They were off drugs interfering with 5HT metabolism at least for one month.

Study was carried out according to Declaration of Helsinki, after the approval by the Institutional Ethic Board all subjects signed an informed consent to participate in the study. Healthy volunteers and conservatively treated patients were studied during hospitalisation under basal conditions. Blood specimen (5 ml) were sampled from antecubital vein from each participant in the morning hours (7.00—9.00) after fasting overnight. Two hours urine portion was collected after 2 h rest.

In hemodialyzed patients blood was obtained from arterio-venous fistula immediately before and in 6 patients also after hemodialysis.

Conditions of urine collection, blood sampling, preparation of platelet rich (PRP) and platelet free (PFP) plasma and determination of 5HT and 5HIAA by an HPLC method with electrochemical detection were carried out as described previously in detail (Šebeková et al., 1992). Serum creatinine concentration was determined by a standard method using commercial kits (Lachema, Brno, Czech Republic). Creatinine clearance (CCr), factional excretion (FE), glomerular filtration (GF), tubular secretion (TS) and proportion of intrarenal 5HIAA synthesis were calculated. FE was calculated as the ratio of the clearance of 5HT or 5HIAA to that of the creatinine. Concerning the mechanism of the renal excretion following was presumed: FE<1 indicated glomerular filtration and tubular reabsorption, if FE=1 pure glomerular filtration was considered, FE=1—5 indicated glomerular filtration and tubular secretion of 5HIAA, FE>5 was considered as an indirect evidence of its intrarenal production. If FE-5HIAA>1, the theoretical amounts excreted by GF and TS were calculated from known FE and renal excretion (RE) as follows:

$$TS_{5HIAA} = \frac{Fe_{5HIAA}-1}{FE_{5HIAA}} \times RE_{5HIAA} \quad (1)$$

$$GF_{5HIAA} = RE_{5HIAA} - TS_{5HIAA} \quad (2)$$

Relative values of GR and TS were obtained by their division by the value of clearance of endogenous creatinine. Per cent of intrarenal 5HIAA production was estimated according to formula:

$$\text{5HIAA renal production} = \frac{100 \times (FE_{5HIAA}-5)}{FE_{5HIAA}} \quad (3)$$

Results were expressed as mean, median and SD. Means between the groups were compared using analysis of variance, if ANOVA indicated $p<0.05$, post hoc least square differebce test was employed. Pre- to postdialysis values were compared by Wilcoxon's matched-pairs signed rank test. Statistical significance was determined to be at the $p<0.05$ level. Correlation and regression analyses were peroformed (Tallarida and Murray, 1986).

Results

Blood

Serotonin: 5HT concentration in PRP (corresponding to whole blood 5HT level) was decreased in patients in CRI if compared with the healthy volunteers (Tab. 1). However, the mean platelet 5HT content showed no significant changes in CRI, in spite of the lower platelet count. Correlation between 5HT concentration in PRP and platelet count fitted to exponential function ($r=0.678$, $p<0.000001$, all subjects), pointing to the fact, that platelet count

Tab. 1. Parameters of peripheral serotonin metabolism.

		Controls Kontroly (n=60)	CRI Conservat. Therapy Konzervat. liečba (n=14)	CRI Hemodialysis Hemodialýza (n=12)
Ccr [ml/s]	Mean	1.91	0.47	0.15
	Median	1.87	0.44	0.14
	SD	0.57	0.26	0.05
	P	–	0.01.	0.01
5HT-PFP [nmol/l]	Mean	42.0	98.3	88.8
	Median	38.5	67.3	56.7
	SD	23.8	82.4	83.5
	p	–	0.01	0.01
5HT-PRP [nmol/l]	Mean	1330.4	589.0	668.6
	Median	1053.9	680.0	658.8
	SD	1218.0	242.4	322.22
	p	–	0.05	0.05
5HT/Plt [nmol/10^9]	Mean	2.60	2.14	2.18
	Median	2.29	1.77	2.21
	SD	1.91	1.23	0.70
	p	–	NS	NS
5HT-U [nmol/h]	Mean	37.99	11.50	1.56
	Median	28.50	8.50	1.50
	SD	37.00	8.39	1.36
	p	–	0.01	0.01
FE5HT	Mean	0.156	0.101	0.064
	Median	0.104	0.067	0.066
	SD	0.146	0.083	0.044
	p	–	NS.	0.05
Platelet count [x*10^9/l]	Mean	472	330	217
	Median	509	330	200
	SD	157	129	66
	p	–	NS	0.01

Ccr: creatinine clearance, 5HT-PFP: serotonin concentration in platelet free plasma, 5HT-PRP: serotonin concentration in platelet rich plasma, 5HT/Plt: platelet serotonin concentration, 5HT-U: serotonin urinary excretion, FE5HT: fractional excretion of serotonin, Plt count: platelet count in platelet rich plasma, NS: not significant

Ccr: klírens endogénneho kreatinínu, 5HT-PFP: koncentrácia serotonínu v plazme bez doštičiek, 5HT-PRP: : koncentrácia serotonínu v plazme bohatej na doštičky, 5HT/Plt: koncentrácia serotonínu v doštičkách, 5HT-U: vylučovanie serotonínu do moča, FE5HT: frakčná exkrécia serotonínu, Plt count: počet doštičiek v PRP, NS: nevýznamné

Tab. 2. Parameters of peripheral 5HIAA metabolism.

		Controls (n=60)	CRI Conservat. Therapy Konzervat. liečba (n=14)	CRI Hemodialysis Hemodialýza (n=12)
5HIAA-PFP [nmol/l]	Mean	37.4	432.9	742.2
	Median	32.7	315.9	462.7
	SD	19.3	335.4	571.0
	p	–	0.01	0.01
5HIAA-U [μmol/h]	Mean	0.86	0.97	0.29
	Median	0.84	0.91	0.25
	SD	0.41	0.43	0.14
	p	–	NS	0.01
		(n=56)	(n=9)	(n=5)
FE5HIAA	Mean	3.91	3.06	0.94
	Median	3.51	1.76	0.94
	SD	2.34	3.95	0.61
	p	–	NS	0.01
GF 5HIAA [μmol/h]	Mean	0.258	0.206	0.135
	Median	0.238	0.135	0.140
	SD	0.15	0.139	0.055
	p	–	NS	NS
GF/Ccr [l/h]	Mean	0.038	0.294	0.492
	Median	0.032	0.310	0.301
	SD	0.023	0.167	0.310
	p	–	0.01	0.01
TS 5HIAA [μmol/h]	Mean	0.617	0.571	0.067
	Median	0.588	0.310	0.082
	SD	0.374	0.964	0.055
	p	–	NS	0.01
TS/Ccr [l/h]	Mean	0.093	0.514	0.294
	Median	0.081	0.295	0.310
	SD	0.063	0.507	0.220
	p	–	0.01	0.01

5HIAA-PFP: concentration of 5-hydroxyindole-3-acetic acid in platelet free plasma, 5HIAA-U: renal excretion of 5-hydroxyindole-3-acetic acid, FE 5HIAA: 5HIAA fractional excretion, GF: glomerular filtration, TS: tubular secretion

5HIAA-PFP: koncentrácia 5-hydroxyindoloctovej kyseliny v plazme bez doštičiek, 5HIAA-U: renálna exkrécia 5-hydroxyindol-3-octovej kyseliny acid, FE 5HIAA: frakčná exkrécia 5HIAA, GF: glomerulárna filtrácia, TS: tubulárna sekrécia

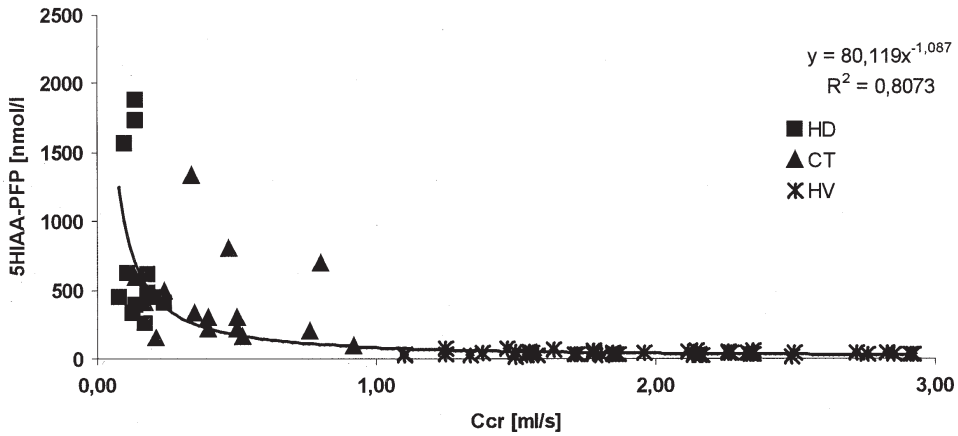

Fig. 2. Relationship between 5HIAA concentration in plasma and creatinine clearance. 5HIAA — 5-hydroxy-3-indoleacetic acid concentration in platelet free plasma, Ccr — creatinine clearance, HD — hemodialyzed patients, CT — conservatively treated patients in chronic renal insufficiency, HV — healthy volunteers.

Tab. 3. The effect of hemodialysis on concentrations of creatinine, parameters of blood serotonin and 5HIAA and platelet count in platelet rich plasma.

		PREDIALYSIS Pred HD (n=6)	POSTDIALYSIS Po HD (n=6)
S-creatinine [μmol/l]	Mean	945.28	493.62
	Median	896.75	451.15
	SD	252.20	216.98
	P		0.0008
5HT-PFP	Mean	95.52	87.68
[nmol/l]	Median	87.75	65.12
	SD	38.50	86.79
	P		NS
5HIAA-PFP	Mean	1043.68	701.70
[nmol/l]	Median	1087.31	662.77
	SD	695.01	421.76
	P		NS
5HT-PRP	Mean	822.87	568.88
[nmol/l]	Median	788.75	617.03
	SD	373.73	155.51
	P		NS
5HT/Platelet	Mean	2.47	2.14
[nmol/10^9l]	Median	2.25	1.77
	SD	0.78	0.65
	p		NS
Platelet count	Mean	230.3	228.0
[x.10^9/l]	Median	228.0	218.0
	SD	30.3	25.2
	p		NS

5HT: serotonin, 5HIAA:5-hydroxy-3-indoleacetic acid, PFP: platelet free plasma, PRP: platelet rich plasma
HD: hemodialýza, 5HT: serotonín, 5HIAA:5-hydroxy-3-indoloctová kyselina, PFP: plazma bez doštičiek, PRP: plazma bohatá na doštičky

is limiting factor of the whole blood 5HT level. In spite of the decreased 5HT concentration in PRP approximately two-fold increase in 5HT concentration in PFP was revealed in CT and HD patients if compared with the control group.

5HIAA: 5HIAA accumulated in plasma in CRI (Tab. 2), 5HIAA levels started to increase if Ccr<0.3 ml/s (Fig. 2).

The effects of hemodialysis on accumulated 5HT and 5HIAA: Data on pre- and posthemodialysis concentrations of creatinine in serum, 5HT and 5HIAA in PFP, 5HT in PRP, platelet 5HT content and platelet count in PRP are in Table 3. Dialysis did not eliminate the cumulated plasma 5HT and 5HIAA effectively. The pretreatment 5HIAA PFP concentrations correlated with their change in the course of hemodialysis ($r=0.819$, $p<0.05$).

Serotonin: Renal excretion: Regardless of the increased filtration load the renal excretion of 5HT decreased in CRI (Tab. 1). Urinary 5HT excretion correlated with Ccr (Fig. 3). Fractional excretion: FE-5HT was decreased in patients with CRI (Tab. 1). Correlation was found between FE-5HT and Ccr ($r=0.578$, $p<0.000001$). In all subjects FE-5HT<1, pointing to the reabsorption of 5HT in proximal tubules, or its local degradation into 5HIAA.

5HIAA: Renal excretion: Due to the increased filtration load the renal excretion of 5HIAA in CT patients with CRI was even higher than that of the healthy volunteers. Decrease was observed in HD patients only (Tab. 2). Urinary 5HIAA excretion correlated with Ccr ($r=0.455$, $p<0.00002$). Fractional excretion: In course of the CRI FE-5HIAA decreased (Tab. 2). FE-5HIAA correlated with Ccr ($r=0.554$, $p<0.000001$). In 13 out of the 60 investigated healthy subjects and in 2 out of the 14 CT patients in CRI FE-5HIAA>5 (chi^2, p: NS). This pointed indirectly to intrarenal 5HIAA production. The theoretical calculated intrarenal production varied between 1.2—66. 1 per cent of the total excreted amount of 5HIAA in the studied group. Glomerular filtration and tubular excretion: The absolute values of 5HIAA excreted via glomerular filtration did not differ between the groups (Tab. 2). The participation of TS in 5HIAA renal excretion was decreased in HD patients. However, the relative participation of GF in 5HIAA excretion increased by decreasing renal function (7.7 times in CT and 12.9 times in HD patients in comparison to healthy volunteers). Participation of TS showed moderate increase in comparison with that of the GF. While in healthy subjects the ratio of 5HIAA GF to TS in 5HIAA renal excretion was approximately 30:70, in HD patients a reversal of this ratio (67:33) was revealed.

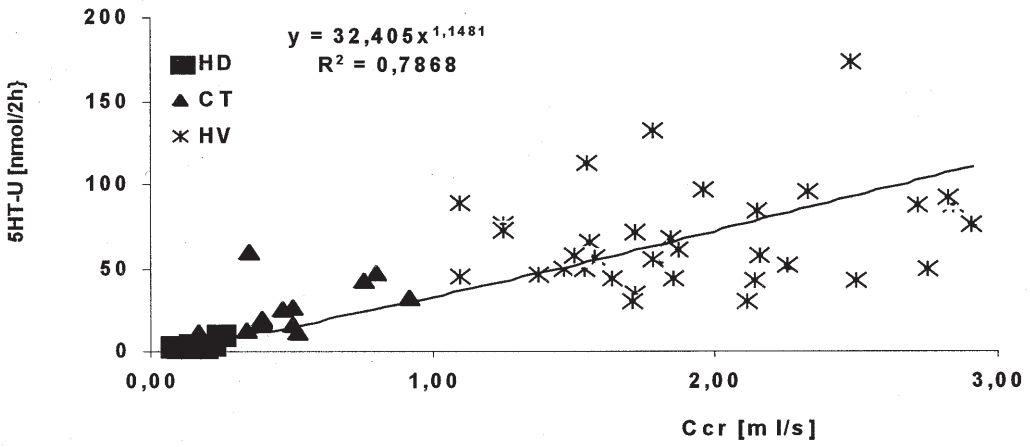

Fig. 3. Relationship between serotonin urinary excretion and creatinine clearance. 5HT-U — serotonin urinary excretion, Ccr — creatinine clearance, HV — healthy volunteers, CT — conservatively treated patients, HV — hemodialyzed patients in chronic renal insufficiency.

Discussion

5HT and 5HIAA balance in CRI: In CRI patients the amount of 5HIAA excreted to urine is not changed significantly if compared to healthy subjects, indicating the adequate peripheral 5HT production in CRI. An increased 5HT concentration in PFP as revealed by other authors (Steyn et al., 1992; Minami et al., 1987; Sagripanti et al., 1993; Malyszko et al., 1996) is in accordance with this view.

The main source of 5HT in periphery is in platelets, where it is stored in dense granules. In CRI patients pertubation of platelet 5HT uptake, its release from platelets as well as decreased 5HT dense granule content was reported (Eknoyan and Brown, 1981; Soslau et al., 1990; Barradas et al., 1991; Kanai et al., 1996; Malyszko et al., 2000). Our data point only to an insignificant trend towards lower platelet 5HT content of CRI patients in comparison with healthy subjects. However, because of the decreased platelet count the total amount of stored 5HT is decreased. Data on whole blood 5HT concentration in uremic patients are inconsistent: decline was revealed in some studies (Steyn et al., 1992; Malyszko et al., 1996; Pivac et al., 2001), while elevated concentrations are reorted by others (Kerr et al., 1996; Mydlík et al., 1975).

The PFP 5HT could be eliminated by two mechanisms: a) A small part of 5HT escapes metabolism in blood. It is taken up by the OCTS of proximal tubule and metabolized into 5HIAA which is excreted into urine. Only a negligible part of 5HT is secreted into urine unchanged, because 5HT excreted to urine seems to originate in the kidney (Sole et al., 1986). Decreased 5HT excretion in CRI patients is in accordance with this view. b) The bulk of plasma 5HT is metabolized by endothelial cells to 5HIAA which is taken up by OATS of proximal tubular cells and excreted to urine containing both 5HIAA originating from plasma and that produced in proximal tubular cells.

The insufficient kidney is unable to excrete sufficient amounts of 5HIAA, therefore plasma concentration of 5HIAA increases. As a result the amount of 5HIAA filtered in glomeruli increases and so does the glomerular/tubular excretion ratio. This is the main alteration in the excretion of 5HIAA that develops with the decreasing kidney function.

The effect of hemodialysis: The elimination of 5HT and 5HIAA by hemodialysis shares a great individual variability. In the present study only insignificant changes were revealed. However, the higher the predialysis value, the greater fall in plasma concentration was evident. The obtained results are contradictory to those of others who reported effective elimination of 5HT by dialysis (Minami et al., 1987; Kerr et al., 1992), or event its increase (Mydlík et al., 1975). The following factors might participate: a) platelet activation and/or aggregation with 5HT release and its degradation to 5HIAA; b) liberation of 5HT and 5HIAA from transport proteins during hemodialysis; c) competition of free fatty acids on protein binding; d) other factors, such as residual renal function, hemoconcentration in course of dialysis, etc.

Clinical relevance: At least the most important implications will be mentioned: a) 5HT is a prostaglandine-synthetase independent platelet aggregating factor which even amplifies the action of other aggreating modulators (Holmsen, 1985). Thus, the doubled 5HT PFP concentrations increase the platelet aggregability. On the other hand the decreased platelet count (with normal platelet 5HT content) could evoke the decreased platelet trombi formation. These two opposing mechanisms could explain a simultaneous hyper-/hypocoagulability. b) No marked effect of hemodialysis was found in the studied group of patients. However, this action depends on various factors during dialysis, notably on membrane biocompatibility. c) 5HIAA appears not to be an inert metabolic product. It shares various interactions such as albumin binding of various compounds and drugs, compatition at OATS and even inhibiting glucose utilization (Šebeková et al., 1996).

In conclusion, 5HT is produced in normal amounts in CRI patients. However, because of decreased platelet count its storage capacity is decreased. Its PFP concentration doubles. 5HT is metabolized into 5HIAA by endothelial and proximal tubular cells. Its plasma concentration increases with decreasing kidney function and consequently its elimination by glomerular filtration turns to be the dominant mechanism of elimination.

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