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Metabolic Turnover of Biogenic Amines In Physiological Fluids: Diagnostic Significances

[Fizyolojik Sıvılardaki Biyojen Aminlerin Metabolik Döngüsü: Tanısal Önemi]

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ABSTRACT

The term of biogenic amine is an umbrella term that encompasses all amines with an origin in biological processes. This review will be restricted to the biogenic amine abnormalities that affect the metabolism of the catecholamines and serotonin mostly in patients with phaeochromocytoma and carcinoid syndrome, and the inborn errors that primarily affect their metabolism. An idea is also developed that proposes that abnormalities of biogenic amine metabolism are far more common than is currently considered, and that the search for these problems may be appropriate in any neonate or children who presents with neurological problems of unknown origin. Correction of the abnormal neurochemical pattern could predict treatment efficacy. This review article holds the reference values and metabolic ratio of catecholamines, serotonin and their metabolites in the serum, cerebrospinal fluids and urine for healthy persons and values and metabolic ratio of catecholamines, serotonin and their metabolites in patients with phaeochromocytoma and carcinoids syndrome.

Key Words: Catecholamines, serotonin, metabolites, carcinoid tumors, phaeochromocytoma, genetic diseases

ÖZET

Biyolojik amin terimi kökeni biyolojik oluşumlar olan tüm aminleri kapsamaktadır. Bu derleme sadece çoğunlukla feokromositoma ve karsinoid sendrom hastaları ile doğuştan kaynaklanan serotonin ve katekolamin metabolizmasını etkileyen biyolojik amin anormalilerni ele almaktadır. Biyolojik amin metabolizması bozukluklarının tahmin edilenden daha fazla olduğu ve tüm yenidoğanlarda yada kökeni bilinmeyen nörolojik sorunlara sahip tüm çocuklarda bu metabolik bozukluğun araştırılması fikri önerilmektedir. Anormal nörokimyasal modelin düzeltilmesi tedavi etkinliğinin tahminine olanak sağlayabilir. Derleme, hem sağlıklı kişilerde hemde feokromositoma ve karsinoid sendrom hastalarında gözlenen katekolamin, serotonin ve metabolitlerinin serum, serebrospinal sıvı ve idrarda gözlenen referans değerlerini ve metabolik oranlarını içermektedir.

Anahtar Kelimeler: Katekolaminler, serotonin, metabolitler, karsionid tümörler, feokromositoma, genetik hastalıklar

Abbreviations used: AD – aldehyde dehydrogenase; APUD - amine precursor uptake and decarboxilation ; AR – aldehyde reductase [alcohol dehydrogenase, EC 1.1.1.1.]; BH4 – tetrahydrobiopterin; CA – catecholamines; COMT – catechol-O-methyltransferase; CSF - cerebrospinal fluid ; DA – dopamine; DBH – dopamine-β-hydroxylase; DHPG – dihydroxyphenylglycol; DHPR – dihydropteridine reductase; DOPA - L- dihydroxyphenylalanine; DOBA - 3,4-dihydroxybenzoic acid; DOMA - 3,4-dihydroxymandelic acid; DOPAC – dihydroxyphenylacetic acid; E – epinephrine; 5-HIAA – 5- hydroxyindole acetic acid; HMMA - 4-hydroxy-3-methoxymandelic acid; 5- HTP - 5-hydroxytryptophan; HVA – homovanillic acid; LAAAD – L-aromatic aminoacid decarboxylase; MAO – monoamine oxidase; MHPG – methoxyhydroxyphenylglycol; MN – metanephrine; NE – norepinephrine; NMN – normetanephrine; PNMT – phenylethanolamine-N-methyl-transferase; PST – phenolsulfotransferase; 5-HT – serotonin; TH – tyrosine hydroxylase; VAT – vesicular amine transporter; VMA – vanillylmandelic acid.

INTRODUCTION

This review will be restricted to the biogenic amine abnormalities that affects the metabolism of the catecholamines [CA], serotonin [5-HT] and their metabolites, specially in phaeochromocytoma, carcinoids syndrome, and inherited neurogenetic disorders. Second aim of this study was to determine reference values of biogenic amines and metabolites in plasma, cerebrospinal fluid [CSF] and urine of 500 healthy individuals. The pathways of biosynthesis are given in Fig. 1. The enzyme tyrosine hydroxylase [TH] catalyzes the synthesis of L-dihydroxyphenylalanine [DOPA] from tyrosine, which is derived from either diet or synthesized from phenylalanine. The conversion of DOPA to dopamine [DA] is catalyzed by the enzyme aromatic amino-acid decarboxylase. The adrenal medulla and sympathetic nerve endings store DA in the form of cytoplasmatic granules. Norepinephrine [NE] is formed by the action of DA ß-hydroxylase and the enzyme phenylethanolamine-N-methyl transferase converts it to epinephrine [E]. Nerve stimulation causes the release of CA from the storage granules within the chromaffin cells. CA has a very short half-life of approximately two minutes in serum. The major metabolites of interest in laboratory testing are metanephrine [MN] and vanillylmandelic acid [VMA]. NE and E are metabolized to MN through the action of catechol-O-methyltransferase [COMT], and monoamine oxidase [MAO] promotes the final conversion to VMA.

Disorder of the phaeochromocytoma

Until recently, clinical CA neurochemistry has been used mainly to examine release of CA as effector chemicals in the brain and periphery, in order to indicate activities of control and peripheral neuronal system. For example: phaeochromocytomas produce, store, and secrete CA. They are usually derived from the adrenal medulla but may develop from chromaffin cells in or about sympathetic ganglia [extraadrenal phaeochromocytomas or paragangliomas]. Related tumors that secrete CA and produce similar clinical syndromes include chemodectomas derived from the carotid body and ganglioneuromas derived from the postganglionic sympathetic neurons.

The main interest of the adrenal medulla in the clinical chemistry relates to phaeochromocytomas. These are tumors which secrete CA, the normal secretory products of the organ and which are rare, but treatable, cause of hypertension. Approximately ten percent of phaeochromocytomas are found in extramedullary tissue that shares same embryological origin, which is chromaffin tissue derived from neuroectoderm. CA can also be produced by tumors of embryologically related tissue, for example, the carotid bodies, and by neuroblastomas, rare tumors occurring only in infants and young children. These tumors form part of a group known APUD tumors. Patients with phaeochromocytomas usually present with hypertension; although this may be episodic, it is usually sustained. Other features include palpitation, flushing and abdominal discomfort. These tumors are

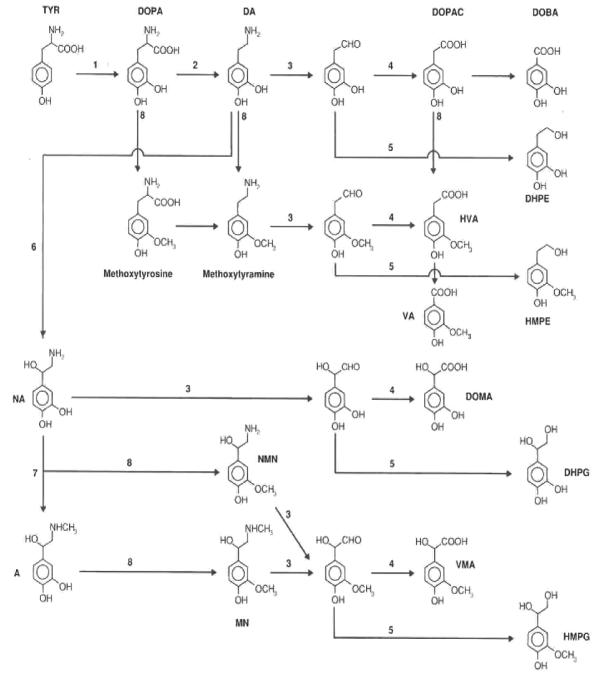

Figure 1. Biosynthesis and metabolism of catecholaminergic transmitters. 1, Tyrosine hydroxylase [located in the cytosol of neurons]; 2, decarboxylase [located in the cytoplasm of most tissues]; 3, monoamine oxidase [located largely on the outer mitochondrial membrane intra- and extraneuronally; oxidative deamination]; 4, aldehyde dehydrogenase [oxidation]; 5, alcohol dehydrogenase [reduction]; 6, dopamine-ß-hydroxylase [membrane-bound in amine storage granules of adrenergic neuron or adrenal chromaffin tissue]; 7, phenylethanolamine-N-methyltransferase [PNMT; cytosolic enzyme of adrenaline synthesizing cells]; 8, catechol-O-methyltransferase [located mainly extraneuronally]. TYR, tyrosine; dopa, 3,4-dihydroxyphenylalanine; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; DOBA, 3,4-dihydroxybenzoic acid; DOMA, 3,4-dihydroxymandelic acid; HVA, homovanillic acid; VA, vanillic acid; VMA, vanillic mandelic acid; DHPE, 3,4-dihydroxyphenylethanol; HMPE, 4-hydroxy-3-metoxyphenylethanol; MHPG, 4-hydroxy-3-metoxyphenylethyleneglycol: MN, metanephrine; NMN, normetanephrine; NA, noradrenaline; A, adrenaline.

rare cause of hypertension [approximately 0.5 % of all cases]. While hypertension itself is common, it is important to have available a screening test that identifies those patients likely to have a phaeochromocytoma, and who should be subjected to more definitive investigation, and that screens out those in whom this probability is very low. The metabolism of CA is outlined in Fig.1. E and NE are metabolized by COMT to metadrenalines [MN] and normetadrenaline [NMT], respectively. They are also converted by the consecutive action of MAO and COMT to 4-hydroxy-3-methoxymandelic acid [HMMA], also known as VMA. Measurement of urinary HMMA is the most reliable screening test although the measurement of total urinary MN is also used [Table 1 and Table 2]. Various foodstuffs, including tea, coffee, chocolate, bananas and vanilla, may react in the screening test for HMMA and should be avoided. Some drugs also interfere in the test, depending on the method used, and advice should be sought from the laboratory before either collecting samples or starting treatment [Table 3].

If the screening test is negative, the diagnosis can be excluded. False negative responses occur only very rarely; they are more likely in a patient whose hypertension is intermittent and it is important that in such cases a urine collection is made at a time when the blood pressure is raised. If the screening test is strongly positive, serum E and NE should be measured [Table 4]. If these levels are raised, localization procedures, such as selective venous cannulation with CA measurements and isotope and CT scanning should be carried out, guided by the fact that extra-adrenal phaeochromocytomas tend to secrete NE in excess of E, the reverse being true of tumors of the adrenal medulla itself. When the screening test is not clearly diagnostic, the pentolinium test may be used as an aid to diagnosis. Pentolinium is sympathetic ganglion-blocking drug that reduces CA secretion in normal subjects but not in patients with phaeochromocytomas; in such patients, secretion is autonomous. Blood is taken for CA content before and fifteen minutes after giving 2.5 mg pentolinium by intravenous injection. Although still potentially dangerous, this procedure is more reliable and less hazardous than the phentolamine test which has been used in the past. This α-adrenergic blocking drug causes dramatic hypotension in patients with phaeochromocytomas. Although phaeochromocytomas are benign in ninety percent of cases, all tumors should be removed surgically. However, this is a potentially hazardous operation since large quantities of CA may be released into the circulation during the procedure. It should be noted that ten percent of patients with phaeochromocytomas have multiple tumors. The tumors may be a component of the Sipple syndrome [multiple endocrine adenomatosis type IIa] and thus evidence of other relevant endocrine disorders should be sought in affected patients. The adrenal medulla produces CA but is not essential to life. There appear to be no clinical sequelae from decreased adrenal medullary activity but tumors of the glands [neuroblastomas and phaeochromocytomas] can produce excessive quantities of CA. These cause hypertension and other clinical features related to increased sympathetic activity.

Table 1. Diagnostic workup of patients for phaeochromocytoma

Select patients with symptoms of pheochromocytoma	Rule out drug and chemical interferences when levels are elevated
Use 24-hour urinary metanephrine assay as a screening test	
Use 24-hour urinary VMA and / or catecholamine tests when urinary metanephrine levels are either borderline or increased	
Reserve plasma catecholamine assays for patients with either borderline or normal urine tests in whom the diagnosis of pheochromocytoma is highly suspected	

Table 2. Urinary metabolite values in phaeochromocytoma

Metabolite	**Normal excretion rate [mg / 24 hours]**	**Usual range in pheochromocytoma [mg / 24 hours]**
Free CA	< 0,1	0,25 - 4,50
MN and NMN	< 1,3	2,80 - 5,00
VMA	< 7,2	15 – 300

Table 3. Interference with tests for phaeochromocytoma

	Urinary metanephrines	**Urinary VMA**	**Urinary Catecholamines**	**Plasma catecholamines**
Physiological variables		Exercise [I] Stress [I]	Exercise [I] Stress [I]	Stress [I]
Drug effects	Chlorpromazine [I] MAO inhibitors [I][S]	Guanethidine [I] Isoproterenol [I] Methyldopa [I] Naladixic acid [I][S	L-Dopa [I][S] Isoproterenol [I] Methyldopa [I][S] Epinephrine [I] Nicotine [I] Reserpine [I]	Aminophylline [I] Chlorpromazine [I] Epinephrine [I] Isoproterinol [I] MAO inhibitors [I] Methyldopa [I] Phenothiazines [I]
	Levodopa [D]	Disulfiram [D][S] Imipramine [D] Levodopa [D] MAO inhibitors [D][S] Reserpine [D] Phenothiazines [D][S]	Cionidine [D] Guanethidine [D] Reserpine [D]	Reserpine [D]
Chemical Interference	Imipramine [I] Phenacetin [I] Phenothiazines [I][S]	Aspirin [I] Bananas [I] Caffeine [I] Chocolate [I]	Aspirin [I] Bananas [I] Erythromycin [I] Formaldehyde [I] Isoproterenol [I]	Amphicillin [I] Epinephrine [I] Levodopa [I] Quinidine [I] Tetracycline [I]
	Propranolol [D][S]	Vanilla [I]	Quinidine [I] Tetracycline [I]	
	Radiograph contrast dye [D][S]	Clofibrate [D][S]	Chlorpromazine [D]	

Modified from several sources [1, 2, 3]
I – increase; S – Marked effect; D – Decrease

Table 5. Tests for phaeochromocytoma: reference intervals

Test	Reference interval
Metanephrines, urine [spectrophotometric]	< 1.3 mg / 24 h
VMA, urine [spectrophotometric]	2 – 7 mg / 24 h
Catecholamines, urine [HPLC]	Epinephrine: < 20 µg / 24 h Norepinephrine: < 80 µg / 24 h
Catecholamines, plasma [radioenzymatic]	Epinephrine: < 75 pg / ml Norepinephrine: < 104-548 pg / ml

Carcinoid tumors

Carcinoid tumors arise from the argentaffin cells of the gut, cells of the amine precursor uptake and decarboxilation [APUD] series; ninety per cent of these tumors are found in the appendix and ileocaecal region but they also occur elsewhere in the gut, gallbladder, biliary and pancreatic ducts, and in the bronchi. They are of low-grade malignancy; while they frequently invade local tissue, distant metastases are rare. The carcinoid syndrome is a result of the liberation of vasoactive amines, such as serotonin and peptides [including substance P], from the tumor into the circulation. It is usually only seen with bronchial tumors, which liberate their products directly into the systemic circulation, or when tumors in the gut have metastasized to the liver. Since the greater part of the gut is drained by the portial circulation, the secreted products of tumors in the gut pass to the liver and are inactivated there. However, the secreted products of hepatic metastases reach the systemic circulation via the hepatic veins. 5-HT is synthesized from tryptophan [Fig 2]. In patients with carcinoid syndrome, fifty percent of dietary tryptophan [rather than the usual one percent] may be metabolized by this pathway, diverting tryptophan away from protein and nicotinic acid synthesis. [Pellagra-like skin lesions due to nicotinic acid deficiency are an occasional feature of the carcinoid syndrome]. The major amine secreted by intestinal carcinoid tumors [derived from embryonic midgut] is 5-HT. Bronchial carcinoids [derived from foregut] tend to produce 5-hydroxytryptophan since they often lack the decarboxylase enzyme. All carcinoid tumors may also produce histamine, kinins and substance P, which are important in the symptomatology of the carcinoid syndrome. Further, the secretion of peptide hormones, including ACTH, calcitonin and other products of cells of the APUD series, is often demonstrable and may contribute to the clinical presentation. 5-HT is the most common secretory product of carcinoid tumors. As shown in Fig 2, carcinoid tumors synthesize 5-HT by enzymatic modification of circulating tryptophan. Up to 50 percent of the dietary intake of tryptophan can be converted to 5-HT by these cells, which may leave inadequate substrate for incorporation into proteins and conversion to niacin. As a result, patients with widely metastatic carcinoid tumors may suffer symptoms of protein malnutrition or mild pellagra. Carcinoid tumors elaborate multiple monoamines and peptide hormones, including histamine, CA, bradykinins, tachykinins, enkephalins and endorphins, vasopressin, gastrin, adrenocorticotrophin, and prostaglandins. Many secrete somatostatin, neurotensin, substance P, neurokinin A, TRH-like peptide [EEP-NH2] and motilin. The elevated circulating levels of these substances mediate many of the pathophysiologic changes of carcinoid syndrome, although the relative contributions of each remain to be identified. The diagnosis of carcinoid tumors is influenced by the presenting features of the tumor. Evaluation of patients with clinical features of carcinoid syndrome is based on the observation that 5-HT is synthesized and secreted by the large majority of functional carcinoid tumors. As shown in Fig 2, 5-HT is metabolized in the blood to 5-HIAA, which is cleared by the kidneys. Plasma and platelet 5-HT and urinary 5-HIAA levels are usually elevated in the setting of carcinoid syndrome [Table 5, Table 6, and Table 7]. Measurement of urinary 5-HIAA excretion is the most useful diagnostic test, and approximately 75 percents excrete more than 80 µmol / d [15 mg / d]. The specificity of this test approaches 100 percent after exclusion of ingested substances known to elevate 5-HIAA levels. In some patients with carcinoid syndrome and normal urinary 5-HIAA, documentation of elevated plasma or platelet 5-HT concentrations may establish the diagnosis. However, many foregut carcinoid tumors lack aromatic L-amino acid decarboxylase and convert 5-hydroxytryptophan [5-HTP] to 5-HT with low efficiency. Since 5-HTP is not metabolized to 5-hydroxyindole acetic acid [5-HIAA], urinary studies may be misleading. These patients may have elevated urinary 5-HT levels, since renal cells contain L-amino acid decarboxylase. Diagnosis in these cases may be confirmed by demonstrating elevated plasma 5-HTP, histamine, or peptide hormone levels, although it frequently rests on the anatomic detection of the tumor itself. Case history: A fifty-year-old women presented with a history of episodic facial flushing and dizziness sometimes accompanied by wheezing respiration. These attacks could occur at any time but she was frequently embarrassed by them at meal times. Investigations: Urinary 5-HIAA excretion 270 µmol / 24 h [normal 10-50 µmol / 24 h]. An isotopic scan of the liver revealed multiple filling defects suggestive of tumor deposits. A distorted hepatic vasculature with evidence of tumor circulation was demonstrated on arteriography, but the primary tumor could not be located. The diagnosis is confirmed by demonstrating an increase in the urinary excretion of 5-HIAA. This usually more than twice the upper limit of normal and may be much greater. Foodstuffs containing 5-HT as bananas, tomatoes or drugs such as reserpine, which stimulate endogenous serotonin release, must be avoided during the urine collection. Conversely, aspirin and L-DOPA ingestion can cause a falsely depressed 5-HIAA level.

Table 5. Diagnostic workup of patients for carcinoid syndrome.

Select patients with symptoms suggestive of Carcinoids syndrome	Rule out drug and chemical interferences when levels are elevated
Use 24-hour urinary 5-HIAA assay as a screening test	
Plasma and platelet 5-HT and urinary 5-HIAA levels are usually elevated in the setting of carcinoid syndrome	
Reserve plasma catecholamine assays for patients with either borderline or normal urine tests in whom the diagnosis of carcinoid syndrome is highly suspected	
Catecholamines, plasma [radioenzymatic]	

Table 6. Urinary metabolite values in carcinoid syndrome

Metabolite	Normal excretion rate [mg / 24 hours]	Usual range in carcinoid syndrome [mg / 24 hours]
5-HIAA	< 6,8	200-800

Table 7. Hormone mediators of carcinoid syndrome

Clinical feature	Frequency [%]	Candidate mediators
Diarrhea	78	5-HT, histamine, prostaglandins, VIP, glucagon, gastrin, calcitonin
Cutaneous flushing	94	5-HT, 5-HTP, kallikrein, NKA, histamine, SK, SP, prostaglandins
Telangiectasia	25	5-HT, histamine
Wheezing	18	Tumor, hepatic enlargement, bowel ischemia [fibrosis]
Abdominal pain	51	5-HT
Heart disease Right-sided Left-sided	40 13	
Pellagra dermatosis	7	Tryptophan depletion [5-HT synthesis]

5-HT: 5-hydroxytryptamine [serotonin]; 5-HTP: 5-hydroxytryptophan; NKA: neurokinin A; SK: substance K; SP: substance P; VIP: vasoactive intestinal peptide. Source: After W Creutzfeldt and F Stockmann, Am J Med 82: 4, 1987.

Clinical biochemist may chose from a wide array of tests to confirm a clinical diagnosis of phaeochromocytoma and carcinoid tumors. Urinary MN, VMA and CA assays measured by spectrophotometric and fluorometric assays represent the basic core of tests, but plasma CA assays have received attention and HPLC and GC technique are replacing the traditional methods [3]. Although phaeochromocytomas are uncommon tumors, theirs is important because surgical removal cures the vast majority of patients and spares them from the harmful effects of hypertension. The diagnosis requires laboratory testing for confirmation of clinical impression, but tests results are significantly altered by preanalytical and physiological factors. A well-informed pathologist can provide valuable assistance to the clinician in selecting the patients for study, choosing the proper test, and interpreting the test results. This report reviews the issues that should be considered when selecting and interpreting tests for diagnosis of phaeochromocytoma. Particular attention has been given to preanalytical and physiological variables that affect test results rather than to technical aspects of the testing procedure. The hypertension of phaeochromocytoma results from the uncontrolled release into the circulation of the CA [NE and / or E] from tumors formed by chromaffin cells. The name of these cells derives from their distinctive brown color when staining with chromic acid. The tumors secrete CA independently and the normal feedback control of biosynthesis is lost. When released, CA increases the force and rate of myocardial contraction, increase insulin secretion, and cause relaxation of intestinal and bronchial smooth muscle cells. Hormonal action is mediated through activation of α- and ß- receptors situated on cell membranes [4]. Approximately 95 % of phaeochromocytomas are found in the adrenal medulla; 2 % are located in other sites between the diaphragm and the pelvic floor, usually at the bifurcation of the aorta; and 3 % are extra-abdominal. The tumors occur at any age and in both sexes. Approximately 90 % arise sporadically and 10 % are inherited as an autosomal dominant trait. In both sporadic and familial cases, approximately 10 % are malignant [4]. Plasma, CSF and urine were obtained from 500 healthy individuals, and 10 patients with phaeochromocytoma and 10 patients with carcinoids syndrome [Table 8, Table 2, and Table 6]. The determination of CA, 5-HT and the metabolites was done using HPLC-ECD, and HPLC-UV methodology. The determination of CA in the CSF and plasma was done using the method of Sofic [5]. NE, E and DA concentrations were measured by high performance liquid chromatography [HPLC] with Amperometric detection [Shimadzu LC-20A Prominence with BASi-4C Amperometric detector, CC-5e Cross-flow cell]. CA were extracted with Al_2O_3, pH 8,6 and separated on a Nucleosil® column 120 - 5 C_{18}, 5 microns, 250 x 8 x 4 mm. As a mobile phase, 0,05 M of sodium phosphate / sodium acetate buffer, pH 3.0 containing sodium dodecyl sulphate and acetonitrile was used. Quantitation was performed with dehydroxybenzylamine as an internal standard. The lower detections limit was 10 pg / 1 ml. Recovery for CA was ≈ 80 %. All solutions were made up in deionized water [Merck, Li Chrosolv], which was especially suitable for a stable baseline. 5-HT, 5-HIAA, DOPAC and HVA were measured according to Sperk, 1982 [6] with a HPLC-system with electrochemical detection [BASi-4C] on RP-18-Bondapack [10 µ] columns [25 cm / diameter 5 mm]. As a mobile phase, 0.1 M sodium acetate / acetic acid buffer, pH 4.5, containing 5 % methanol and 1 mmol EDTA was used.

Table 8. Normal values of CA and their metabolites, 5-HT and their metabolites in the serum, plasma, CFS and urine [5]: HPLC-ECD, HPLC-UV

Serum, Plasma	NA	Ratio HVA / DA :	100-650 pg / ml
	A	125 – 400	5-100 pg / ml
	DA		5-80 pg / ml
	DOPAC		1-4 ng / ml
	HVA		2-10 ng / ml
	5-HT	Ratio 5-HIAA / 5-HT:	5-35 ng / ml
	5-HIAA	0.34 – 0.8	4-12 ng / ml
Cerebrospinal Fluid	NA	Ratio HVA / DA :	30-350 pg / ml
	A	500 – 3000	5-80 pg / ml
	DA		5-110 pg / ml
	DOPAC		0.5-3 ng / ml
	HVA		15-40 ng / ml
	5-HT	Ratio 5-HIAA /5-HT:	0-2 ng / ml
	5-HIAA	13 - 17.5	13-35 ng / ml
Urine	VMA		1-4 µg / ml
	MHPG		1.5-5.5 mg / 24 h
	DOPAC		0.05-0.5 µg / ml
	5-HIAA		0.1-0.8 mg / 24 h
	HVA		0.5-2 µg / ml
			0.6 2.5 mg / 24 h
			0.5-3 µg / ml
			1-6 mg / 24 h
			2.2-6 µg / ml
			2.5-7 mg / 24 h

Genetic Diseases With Specific Catecholaminergic Phenotypes - Synthesis.

Genetic diseases with specific catecholaminergic phenotypes - synthesis are dihydropteridine reductase [DHPR] deficiency, vitiligo, L-DOPA- responsive dystonia, L-aromatic aminoacid decarboxylase [LAAAD] deficiency, Dopamine-ß-hydroxylase [DBH] deficiency, Menkes disease and familial dysautonomia [Table 9]. One purpose of clinical neurochemistry has been to indicate « activities « of CA systems, by assaying levels of the effector compounds or their metabolites in body fluids such as plasma, CSF, urine, or microdialysate. Distinctive patterns in several neurogenetic conditions reflect enzyme deficiencies as direct or indirect effects of gene mutations. These neurochemical patterns can provide potentially important clues to the diagnosis, treatment, and pathophysiology of neurogenetic disorders. Linking genetic abnormalities with molecular mechanisms and clinical manifestations of disease represents a useful new direction in clinical neurochemistry. Understanding the clinical significance of CA phenotypic changes requires detailed knowledge about the sources and meanings of levels of DOPA, CA and CA metabolites in human physiological fluids, such as plasma and knowledge about the chromosomal sites of genes encoding proteins participating in the synthesis, storage, release, metabolism, and recycling of CA. In mammals, CA biosynthesis stems from a single enzymatic step – conversion of the amino acid tyrosine to the catechol aminoacid L-DOPA by TH [EC 1.14.13.41; Fig 1]. Circulating CA seem crucial for normal neurodevelopment, because genetic disorders of CA biosynthesis typically produce severe neurological defects or fetal wastage [7]. Thus, of mice with knockout of the TH gene, ~ 90 % die in utero [8].

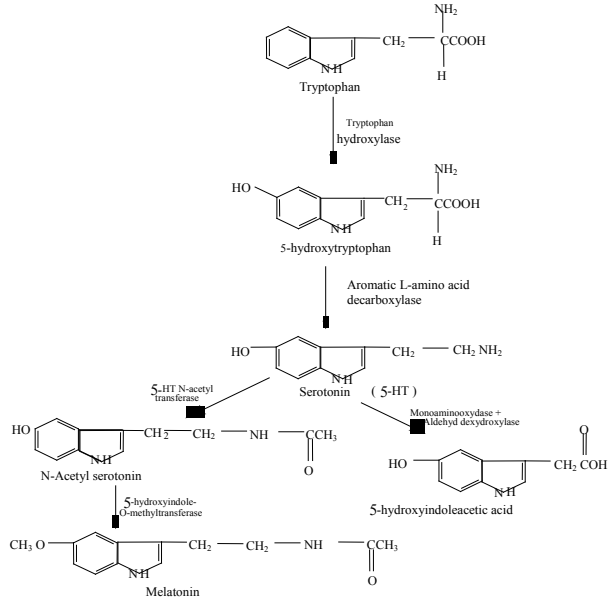

Figure 2. Biosynthesis and metabolism of serotonin

DHPR Deficiency

These clinical problems presumably arise from deficient activities of TH and from defective folate metabolism. Corresponding biochemical consequences include the following: low CSF levels of metabolites of DA, and NE [Fig 1], such as DOPAC, HVA, DHPG, MHPG, and VMA; low CSF levels of the 5-HT metabolite 5-HIAA; and low CSF levels of tetrahydrofolate [9]. Therapy combining phenylalanine restriction with oral administration of L-DOPA, 5-hydroxytryptophan [precursor of 5-HT], and folinic acid appears to improve neurodevelopmental outcomes in DHPR-deficient patients [10,11,12]. At lest 14 different mutations have been described at the DHPR locus [12,13,14,15] on chromosome 4 [16]. Combinations of neurochemical assessment with mutation detection or functional characterization of abnormal DHPR alleles should help elucidate relationships between genotype and clinical phenotype in DHPR deficiency. Moreover, in a patient we studied [11], the pretreatment neurochemical findings [low but detectable plasma levels of DOPA and normal levels of NE, despite absent DHPR activity in erythrocytes and fibroblasts] led to the suggestion of a DHPR-independent mechanism for recycling BH_4, illustrating how neurochemical analyses in patients with rare disorders can also enhance general understanding of CA metabolism.

Vitiligo

Vitiligo is progressive depigmentation. The genetic factors related to these alterations remain unknown. Vitiligo patients have been reported to have increased rates of urinary excretion of HVA and VMA, especially during the onset and in progressive active phases [17] Increased urinary excretion of NE has been noted in some affected individuals [18]. Data concerning plasma CA levels have been inconsistent [18,19], possibly due to a localized catecholaminergic abnormality. Additional genetic and neurochemical studies of patients with this disorder would be useful.

L-DOPA Responsive Dystonia

L-DOPA responsive dystonia, which is inherited as an autosomal dominant trait, includes childhood-onset dystonia, abnormal gait, marked diurnal fluctuation, concurrent or later development of Parkinsonism, and normal cognitive function. It was the pattern of biochemical abnormalities in L-DOPA-responsive dystonia – low brain and CSF levels of DA, HVA, and BH4 [20, 21, 22, 23] – that led initially to the prediction that the disorder would be found to arise from deficient DA synthesis due to decreased tyrosine hydroxylation. Genetic linkage analysis localized the putative mutant gene to chromosome 14q [20], but no candidate genes emerged from the genetic maps, until Ichinose and co-workers mapped the human GTP-cyclohydrolase gene to the L-DOPA-responsive dystonia critical region [24].

L-aromatic aminoacid decarboxylase [LAAAD] deficiency

LAAAD [EC 4.1.1.28] catalyzes the conversion of L-DOPA to DA [Fig 1] and of 5-hydroxytryptophan to 5-HT. The enzyme requires pyridoxal-5'-phosphate [vitamin B6]. A case report describing twins with profound deficiency of this enzyme [25]. Patients with LAAAD had low CSF and plasma levels of monoamines and high levels of DOPA and 5-hydroxytryptophan, from which the authors deduced the underlying enzymatic defects. As the parents each had intermediate LAAAD enzyme activity, the neurochemical findings suggested heterozygosity for a mutant LAAAD allele. To our knowledge, the exact mutation in this, or any other, inherited form of LAAAD deficiency has not yet been defined. The human gene encoding LAAAD has been mapped to chromosome 7 [26, 27] and cloned. Two protein isoforms, resulting from alternative mRNA splicing, have been identified [28]. As noted for LAAAD deficiency, no specific mutations have been reported to date for patients with congenital absence of DBH. The lack of immunoreactive DBH in plasma or CSF [29] suggests that the underlying molecular defect may involve abnormal expression of the DBH gene, such as by a mutation affecting the DBH promoter, splice junctions, or coding sequence.

Dopamine-ß-Hhydroxylase [Dbh] Deficiency

Although mutant mice lacking DBH [EC 1.14.17.1] die during fetal development [30], humans with absent DBH activity have surprisingly few neurological signs. Orthostatic hypotension invariably occurs [31], associated with extremely low or absent concentrations of NE, DHPG, VMA, and MHPG and increased concentrations of DA; DOPAC, HVA, and L-DOPA [32]. The increase in plasma DOPA levels suggests compensatory increased tyrosine hydroxylation in sympathetic nerves [33].

Menkes Disease

Decreased DBH activity in patients with Menkes disease causes a distinctive, abnormal pattern of plasma and CSF catechols [34], with high concentrations of DOPA, DOPAC, and DA, low concentrations of DHPG [an index of intraneuronal NE turnover], and approximately normal concentrations of NE itself consistent with compensatory increases in sympathetic nerve traffic and tyrosine hydroxylation. The neurochemical pattern [in particular, elevated ratios of DOPA / DHPG and DOPAC / DHPG] provides an excellent and biochemical marker for this conditions [34]. Thus, analyses of plasma levels of catechols can diagnose or exclude Menkes disease in at – risk infants during the newborn period, when clinical signs are extremely subtle [35], and other biochemical markers unreliable [36].

Familial Dysautonomia

Patients with this disease have high rates of excretion of HVA and low rates of excretion of VMA [37]. Although this pattern might suggest deficient DBH activity, most of the patients have normal plasma DA and DOPAC levels. Familial dysautonomia patients have high plasma DOPA / DHPG ratios, a failure to increase plasma NE levels during orthostasis [38, 39], and low plasma E levels.

Genetic Diseases with Specific Catecholaminergic Phenotypes: Metabolism

Whereas CA biosynthesis occurs mainly, if not exclusively, by a single pathway [tyrosine hydroxylation], CA inactivation occurs by several alternative pathways that include at least three different intracellular enzymes [Fig. 1]. This diseases includes MAO deficiency, pseudophaeochromocytoma, velo - cardio - facial syndrome, Di George syndrome, von Hippel – Lindau disease and phaeochromocytoma [Table 9].

MAO Deficiency

Several inherited disorders involving MAO deficiency has been described [Table 2]. MAO [EC 1.4.3.4] isoenzymes inactivate CA and their O-methylated metabolites [Fig 1] and also deaminate other biogenic amines, such as 5-HT. The genes encoding the two subtypes of MAO [MAO-A and MAO-B] lie adjacent to each other on the X chromosome. Oxidative deamination of 5-HT depends

Table 9. Chromosomal locations of catecholamine synthesizing, metabolizing, and inactivating genes

	Inactivating Genes	
Protein	Location	Comments
PH	12q-24.1	BH4 cofactor; phenylketonuria
GTP-cyclohydrolase I	14q21-q22	L-DOPA-responsive dystonia
DHPR	4p15.31	Atypical phenylketonuria
Carbinolamine dehydratase	10q22	Mild phenylketonuria
TH	11 [short arm]	Fe enzyme; BH4 cofactor
Tyrosinase	11q14-q21	Cu enzyme; BH4 cofactor
LAAAD	7p13-p11	Pyridoxine cofactor; neonatal seizures, hypotonia
Copper ATPase	Xq13	Menkes disease
DBH	9q34	Cu enzyme; ascorbate cofactor; orthostatic hypotension
PNMT	17	
MAO-A	Xp11.23	Impulsivity, aggressive behavior
MAO-B	Xp11.4	Norrie disease [contiguous gene syndrome]
COMT	22q11.1-11.2	
PST	16p11.2	
NE transporter	16q12.2	Na+-dependent
DA transporter	5p15.3	Na+-dependent
VAT-1 [adrenal]	8p21.3	
VAT-2 [brain]	10q25	
AR	?	
AD	1q32-q42, 3p12, 7q31-q35 9q22 11p14-p15 13q14-q21	

PH-phenylalanine hydroxylase; VAT-vesicular amine transporter.
Source: After Goldstein DS et al., J Neurochem 67: 1781-1790, 1996

on MAO-A; in vitro, both subtypes deaminate DOPA, DA, and NE. A kindred of Dutch men with impulsivity, aggressiveness, and antisocial behavior had isolated deficiency of MAO- A [40], with a point mutation in exon 8 of the MAO-A gene [41]. The patients had increased urinary excretion of NMN, HVA and VMA. The Norrie disease gene is contiguous with the two MAO loci at Xp 11.4-p11.3 [3,094, 3,075], the order from centromere to telomere being Norrie disease / MAO-B / MAO-A. Norrie disease patients can have deletions that include the Norrie disease locus and either the MAO-B locus or both MAO loci [42]. Two brothers with Norrie disease and selective MAO-B deficiency had minimal neurochemical alterations and no behavioral or psychomotor abnormalities. In contrast, a patient with deletion of all three loci had markedly increased levels of O-methylated amine metabolites and low levels of deaminated CA, with severe mental deficiency, autistic-like behavior, atonic seizures, and altered peripheral autonomic function [43]. The findings imply that MAO-A deficiency produces far more serious clinical consequences than does MAO-B-deficiency.

Pseudophaeochromocytoma

Pseudophaeochromocytomas are adrenal tumors that synthesize and secrete CA. In this disease the patients have clinical findings consistent with phaeochromocytoma, but instead of harboring the tumor, the patients have decreased plasma levels of conjugated CA. Because sulfconjugation figures prominently in the inactivation of circulating CA, especially DA [44,45], these patients might have a deficiency of phenolsulfotransferase [PST; EC 2.8.2.1]. Plasma levels of DA sulfate vary widely across individuals and species [46]; consistent with polymorphism in the PST gene [47]. Patients with complete deficiency of PST have not been described to date; the gene encoding PST was cloned [47]. The location is near the gene responsible for Batten disease, an autosomal recessive disorder of lipofuscin metabolism [48].

Velo-Cardio-Facial Syndrome and Digeorge Syndrome

Velo-cardio-facial syndrome and DiGeorge syndrome have been associated with interstitial deletions of chromosome 22q11 [49]. Chromosome 22q11 includes the locus of gene encoding COMT; EC 2.1.1.6. Thus, one may hypothesize that some patients with the Velo-cardio-facial syndrome or DiGeorge syndrome may have only one functional COMT allele and decreased COMT activity [50]. Abnormal ratios of O-methylated to deaminated metabolites of CA in plasma or urine could detect this. The relationship between COMT activity and clinical features of either syndrome remains unknown.

Von Hippel-Lindau Disease and Pheochromocytoma

Von Hippel-Lindau disease is an autosomal dominant disorder. Von Hippel-Lindau disease patients with pheochromocytoma can have false negative results of screening tests based on plasma levels or urinary excretion of CA or CA metabolites, and measurement of plasma free [unconjugated] NMN and MN appears to provide a more sensitive biochemical marker [51]. Pathogenetic of these diseases see in Table 9.

CONCLUSIONS

The wealth of knowledge regarding the synthesis and fate of CA and 5-HT, the availability of sensitive specific HPLC- ECD, and HPLC-UV / VIS assay for L-DOPA, CA, 5-HT and most of their metabolites, and recent ad-

vances in molecular genetic afford the opportunity to glean new understanding of disturbed metabolism of biogenic amines in the patients with pheochromocytoma, carcinoids syndrome, neurological, psychiatric and neurogenetic disorders that involve CA metabolism. This review has presented results of analysis of CA, 5-HT and their metabolites in the serum, CSF and urine. CA, 5-HT and their metabolite values in urine and serum increase in patients with pheochromocytoma as show bellow: free CA normal excretion rate [mg / 24 h] < 0.1; usual range in our patients with pheochromocytoma [mg / 24 h] 0.25 to 4.5. Furthermore, MN and NMNN < 1.3 normal excretion rate [mg / 24 h], and usual range in our patients with pheochromocytoma [mg / 24 h] 2.8 to 50. Values for VMA normal excretion rate [mg / 24 h] < 7.2; usual range in our patients with pheochromocytoma [mg / 24 h] 15 to 300. Analysis of 5-HIAA is used mainly to screen for carcinoid tumors. Urine 5-HIAA levels reflect plasma concentrations of 5-HT. This powerful vasopressin is produced by argentaffin cells and is metabolized through oxidative deamination into 5-HIAA. Normally, urine 5-HIAA values are less than 6 mg / 24 h. Markedly elevated urine 5-HIAA levels as 200 to 800 mg / 24 h were found in our patients with carcinoid syndrome. This finding indicates a carcinoid tumor. Also, this review has presented reference values of CA, 5-HT and their metabolites in the serum, CSF and urine for 500 healthy persons. Serum or plasma contains on the average NE from 100-650 pg / ml, E from 5-100 pg / ml, DA 5-80 pg / ml, DOPAC 1-4 ng / ml, HVA 2-10 ng / ml, 5-HT 5-35 ng / ml and 5-HIAA 4-12 ng / ml . CFS contains NA 30-350 pg / ml, E 5-80 pg / ml, DA 5-110 pg /ml , DOPAC 0,5-3 ng / ml , HVA 15-40 ng / ml, 5-HT 0-2 ng / ml and 5-HIAA 13-35 ng / ml. Urine contains VMA 1,5-5,5 mg / 24 h, 3-methoxy-4-hydrophenylglycol 0,1-0,8 mg / 24 h, DOPAC 0,6-2,5 mg/ m24 h, 5-HIAA 1-6 mg / 24 h, and HVA 2,5-7 mg / 24 h.

Concentrations of NE and E in the plasma are higher than in the CSF, but HVA and 5-HIAA are lower than in the CSF. DA and 5-HT turnover can be approximately expressed by an index of HVA / DA and of 5-HIAA / 5-HT. HVA / DA -ratio and 5-HIAA / 5-HT-ratio are significantly higher in the CSF than in the plasma. Distribution and metabolism of biogenic amines and 5-HT is organ and body fluid specific and uneven. Because reference values are affected by many variables, the range used at our laboratories [Vienna, Wuerzburg, Sarajevo] may not be absolute appropriate for other institutions. Correction of the abnormal neurochemical pattern could predict treatment efficacy.

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