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# BIOCHEMICAL FUNCTIONS AND CLINICAL IMPORTANCE OF UNCONJUGATED PTERIDINES

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**Summary**. *Tetrahydrobiopterine ($BH_4$) and its relatives are classified as unconjugated pteridines or pterins distinguishing them from the folates. $BH_4$ is not a vitamin for mammals, since they can synthesize it. GTP is the major precursor of atoms in the pterin nucleus. The initial step in this pathway is conversion of GTP to D-erythro-7, 8-dihydroneopterin triphosphate, a reaction catalyzed by the enzyme GTP-cyclohydrolase I (EC 3.5.4.16; GTP-CH). There are many important metabolic functions of $BH_4$: it is a crucial cofactor in hydroxylation reactions of phenylalanine, tyrosine and tryptophane. The finding of $BH_4$ participation in monoaminergic neurotransmitter metabolism regulation contributed to the knowledge of atipic neurological symptoms in some kinds of "phenylketonuric" children. As a cofactor of nitric oxide syntheses $BH_4$ is a crucial metabolite involved in physiological function of cardiovascular system. The literature data confirm that the $BH_4$ depletion is crucial in the control of both NO and superoxide generation ($H_2O_2$), synthesized by endothelial NOS isoforms, and consequently the formation of cell toxic peroxynitrite ($ONOO^-$). Relationships between biosynthesis of $BH_4$ and guanine nucleotide regulatory proteins (G proteins) or GTP-binding proteins taking part in protein synthesis has to be explained. The idea that all oxidases using molecular oxygen and producing $H_2O_2$ need $BH_4$ appears rather relevant and it may explain more successfully the polyamine oxidase activity (PAO) in the regulation of polyamine metabolism.*

**Key words**: *Unconjugated pteridines, $BH_4$, metabolic function, GTP binding proteins, polyamines, clinical disorders*

## Introduction

For a long time the investigation of pteridines has been focused on obtaining knowledge about biochemical functions of folic acid and its conjugates, composing the group of *conjugated pteridines*, the compounds with the key role in the nucleic acid (RNA and DNA) synthesis. In humans, tetrahydrobiopterin ($BH_4$), the most important nonconjugated pteridin, differs in *de novo* biosynthesis contrary to folic acid as vitamin (1). The study of biosynthesis and biochemical roles of nonconjugated pteridines has been started in 1959, when $BH_4$ has been recognized as cofactor of aromatic amino acids hydroxylases (1,2). Its involvement in hydroxylation reactions of phenylalanine, tyrosine and tryptophan, as the cofactor of phenylalanine hydroxylase and other specific hydroxylases of the mentioned amino acids, has become the sphere of interest in the last decade when $BH_4$ biosynthesis and degradation pathways were recognized. The participation of $BH_4$ in monoaminergic neurotransmitter metabolism regulation has given the rise to the knowledge of atipic neurological symptoms in some kinds of "phenylketonuric" children (2,3).

Beside this knowledge, since 1979 a number of publications has documented the anomalies in nonconjugated pteridines metabolism in patients suffering from malignant diseases, in which there was a characteristically elevated urinary excretion of neopterin, intermediary product of $BH_4$ synthesis. These reports have potentiated the role of neopterin as the marker" of immune system stimulation". All these articles point out the importance of human "**biopterines**" metabolism research.

## Metabolism of unconjugated pteridines

### Biosynthesis

In 1963 it was postulated that $BH_4$ is synthesized *de novo* in organism. Up to now it has not been revealed if all human tissues could or could not produce the necessary tetrahydrobiopterin quantities in situ. **Guanosin triphosphate (GTP)** has been identified as the precursor in tetrahydrobiopterin synthesis (Fig.1). The initial and key enzyme in this synthesis, GTP cyclohydrolase I (EC 3.5.4.16), was purified and characterized in 1987 by Japanese scientist Takikawa and his collaborators (3). In the first reaction GTP accepts a water molecule and with loosing formic acid is transformed into **dihydroneopterin-triphosphate**. Then it looses phosphate being transformed into **6-pyruvoyl-tetrahydropterin** under the influence of *6-pyruvoyl-tetrahydropterine synthase (6-PTS)*. By the action of *6-pyruvoyl-tetrahydropterin reductase (PTHR*) this compound is reduced into **6-lactoyl-tetrhydropterin,** which produces **tetra-**

**hydrobiopterin ($BH_4$)** under the influence of *sepiapterin reductase*, (Figure 1) (2-5).

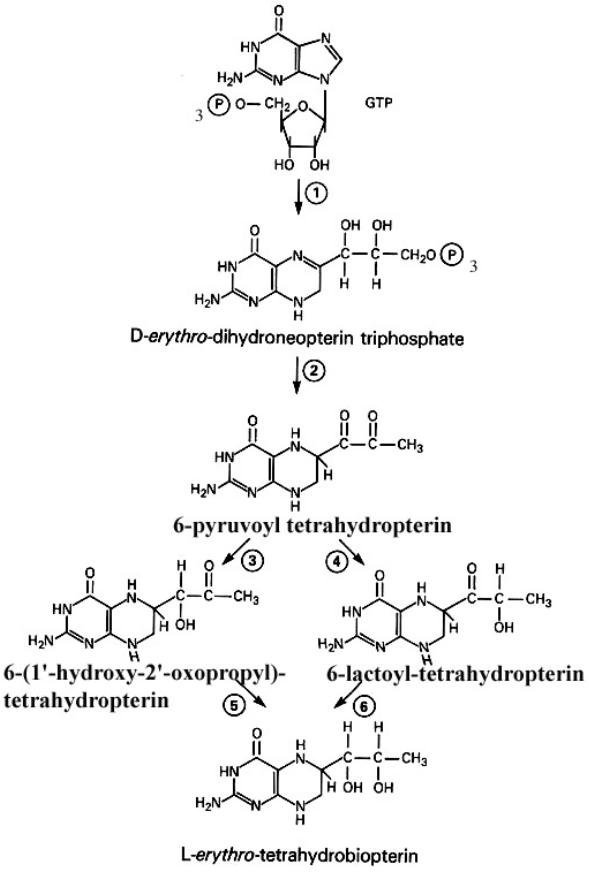


Fig. 1. Biosynthetic pathway of tetrahydrobiopterin (7). 1. GTP-cyclohydrolase, 2. 6-pyruvoyl-tetrahydropterin synthase, 3. sepiapterin reductase, 4. 6-pyruvoyl-tetrahydropterin reductase, 5. sepiapterin reductase, 6. 2'-keto reductase

The immunohistochemical studies on GTP-CH and PTP synthase revealed a nuclear localization for these two $BH_4$ biosynthetic enzymes (4).

GTP-CH activity modulates both the intracellular level of GTP and GFRP (GTP cyclohydrolase I feedback regulatory protein) (4).

The role of tetrahydrobiopterin as the cofactor in hydroxylation reactions of cyclic amino acids is the best described as the part of phenylalanine hydroxylase system (6). PAH system is composed of three essential components - enzyme phenylalanine hydroxylase (PAH), dihydropteridine reductase (DHPR) and nonconjugated pteridine, tetrahydrobiopterin ($BH_4$). Physiological function of $BH_4$ is linked to its ability to reduce molecular oxygen; $BH_4$ provides electrons and as a consequence it is transformed into 4-α-hydroxytetrahydrobiopterin. This compound is dehydrated into quinonoid dihydrobiopterin - $qBH_2$ under the influence of the enzyme *carbinolamine dehydratase* (pterin-4a-carbinolamine dehydratase -PCD; EC 4.2.1.96). $BH_4$ is regenerated through the reduction of $qBH_2$ by the action of the enzyme *dihydropterin reductase* (DHPR; EC 1.6.99.7) with NADH or NADPH as coenzyme; this coenzyme cycles between the tetrahydro and the $qBH_2$ derivative during the hydroxylation treaction (Fig. 2). Dihydropteridine reductase is an essential enzyme in the hydroxylating system for phenylalanine, tyrosine, and tryptophan. In contrast to PAH, DHPR is widely distributed in tissues (7). Whereas its occurrence in brain and adrenal medulla is not surprising in view of its role in the tyrosine hydroxylation system in these tissues, and in the tryptophane hydroxylation system in brain, DHPR should be found in tissues such as heart, kidney and lungs which have little or no aromatic amino acid hydroxylating activity. Its wide distribution, together with $BH_4$ hints undiscovered roles for both $BH_4$ and DHPR. In addition to its role in regenerating $BH_4$ it has been proposed that DHPR (together with dihydrofolate reductase) plays role in keeping folate in the tetrahydro form in brain (7).

The newest data concerned to enzymes involved in metabolism of $BH_4$ revealed that the primary structure of PCD is identical with that of protein of the cell nucleus, named dimerization cofactor (DCoH) of hepatocyte nuclear factor 1α (HNF-1α). The tertiary structures of GTP-CH and PTP S revealed in both enzymes a central pore for which the function is still unknown. There is similarity between these pterin-binding enzymes and small GTP-binding proteins in its subsequent dehydratation and reduction (4).

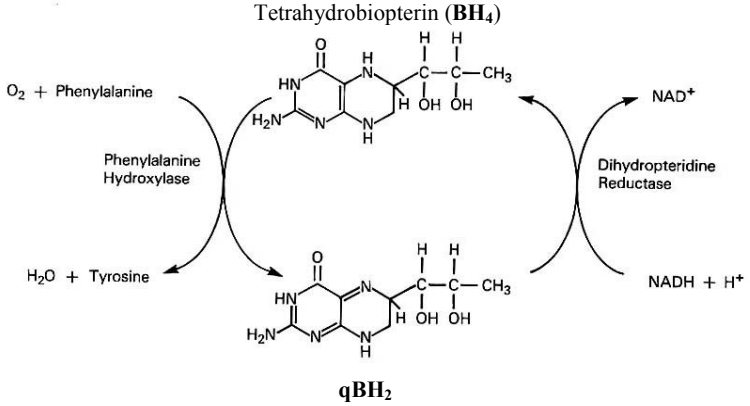


Fig. 2. Regeneratation of $BH_4$

### Catabolism

There are only few, relatively old, reports attempting to explain the possible catabolic pathways of unconjugated pteridines; the difficulties arise from instability of $BH_4$.

The main metabolites are neopterin and biopterin. Neopterin is formed by dephosphorylation of dihydroneopterin triphosphate, the compound produced from GTP by the action of GTP cyclohydrolase. Biopterin is synthesized by $BH_4$ oxidation. The both metabolites are mostly excreted by urine in reduced or oxidized form (1,3).

Up to now, the researches of biosynthesis and metabolic functions of unconjugated pteridines have not discovered any transport protein for $BH_4$, inspite of folic acid whose specific transport protein has been found in blood plasma and cell membrane-folate binding protein (FBP)(8,9). Beside, a number of data point out feeble permeability of cell membrane for $BH_4$; blood-brain barrier seems to be relatively impermeable for $BH_4$, which has been documented in animal experimental models and by mild efficacy in supplementation treatment with $BH_4$ in patients deficient in this compound.

Alimentary income seems neglible because intestinal absorption of $BH_4$ is low in children (12% in average), compared to folic acid absorption-conjugated pteridine (80%) pointing out the side chain of pteridine ring as chemically important component for membrane permeability (1,7).

### Distribution of unconjugated pteridines in biological fluids

A number of nonconjugated pteridines has been identified in human biological fluids. Pteridine urinary excretion depends on age; in the first months of life neopterin and biopterin (N/B) are excreted in 4.2 ratio and 0.53 on adults. The examination of amniotic fluid suggests that this maturation debited from the fetal period. In serum the variations are less pronounced, although the level in cord blood is significantly higher than in children blood. Mother's milk contains significant amounts of biopterin, 90 times higher than in serum, pointing out that mammary glands produce $BH_4$, whose physiological role in newborn nutrition is left to be proven (1).

### Metabolic roles of unconjugated pteridines

$BH_4$ is an essential cofactor of at least five enzymes: *phenylalanine hydroxyl*ase, which catalyses the conversion of phenylalanine to tyrosine, *tyrosine hydroxylase*, necessary for the metabolism of tyrosine to DOPA (a precursor of dopamine, noradrenaline and adrenaline, as well as melanin pigments), *tryptophan hydroxylase*, needed for the synthesis of serotonin and melatonin, all three isoforms *of nitric oxide synthase*, and *alkylglycerol monooxygenase*, which influences ether lipid metabolism. $BH_4$ is a unique cofactor in that its intracellular level, which is determined by its synthesizing enzymes, regulates the activity of all $BH_4$ requiring enzymes, and therefore the levels of important hormones and neurotransmitters. The cofactor function of $BH_4$ in the hydroxylation reactions of aromatic amino acids is related to its ability to reduce molecular oxygen; $BH_4$ provides electrons and in turn is oxidized to $qBH_2$ (7).

The other roles of $BH_4$ have been noticed: hydroxylation of proline, methemoglobin reduction and the role in mitochondrial oxidoreduction. It has been also suggested that it is possible that DHPR could partly provide folate reduction into tetrahydrofolate (THF) in brain, where dihydrofolate reductase (DHFR) activity is rather low. Renal tissue is bigger producer of tetrahydrobiopterin compared to liver tissue. However, no precise role of biopterin has been proved in kidney with possibility that biopterin takes part in diuresis (1). High concentration of pteridines in renal tissue may aggravate the anemia of inflamation (10).

## The role of tetrahydrobiopterin ($BH_4$) in nitric oxide synthase (NOS)

### Structure and function

In the tissues three different genes for three isoforms of NOS exist: neuronal or NOS I, macrophagal or inducible (NOS-II) and endothelial or NOS-III. By the action of nitric oxide synthase, in the presence of molecular oxigen ($O_2$) and NADPH L-arginine converts to L-citrulline and nitric oxide (NO). Tetrahydrobiopterin ($BH_4$) serve as a NOS cofactor for all three isoforms of NOS acting as a redox switch in the catalytic mechanism of the enzyme and allowing electron transfer from the prosthetic heme to L-arginine. The oxygen atoms incorporated into both L-citrulline and NO are derived from atmospheric oxygen (11-13).

The literature data refer that the $BH_4$ depletion is crucial in the control of both NO and superoxide generation ($H_2O_2$) by endothelial NOS isoforms, and the consequently on the formation of cell toxic peroxynitrite ($ONOO^-$) (14).

Today, there is a growing scientific data referred to the significance of $BH_4$ for NOS functions, $H_2O_2$ and peroxynitrite production, respectively (15-17).

A deficiency of $BH_4$ results in eNOS uncoupling, which is associated with, increased superoxide and decreased NO production. $BH_4$ has been suggested to be a target for oxidation by peroxynitrite ($ONOO^-$) and ascorbate has been shown to preserve $BH_4$ levels and enhance NO production; mechanisms underlying these processes remain poorly defined. The immediate product of the reaction between $ONOO^-$ and $BH_4$ was trihydrobiopterin radical ($BH_3$) which may be reduced back to $BH_4$ by ascorbate (18).

### Biosynthesis of $BH_4$ and the immune response

There is an interesting correlation between the cellular response to infections and pterin metabolism.

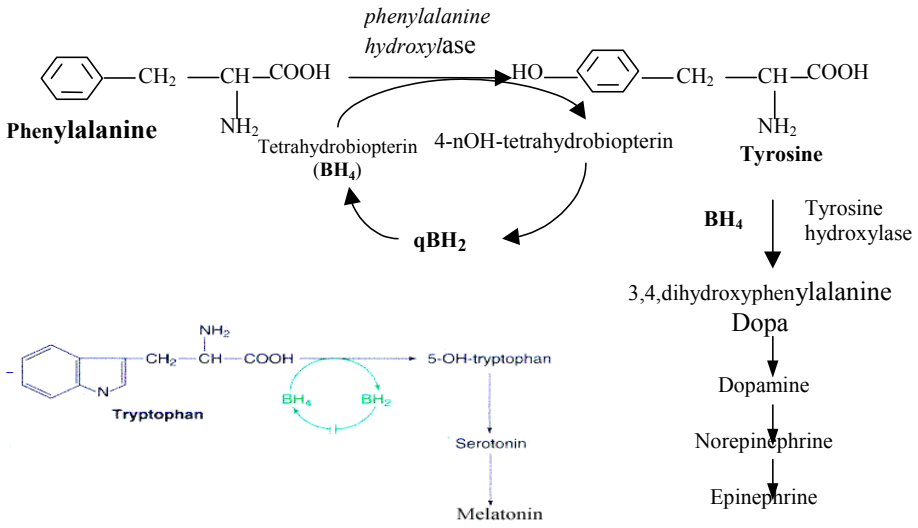


Fig. 3. Biochemical roles of $BH_4$

Neopterin is produced and secreted by interferon-gamma-stimulated monocytic cells (1). Activated macrophages generate and release pteridines. T lymphocyte, but not macrophages, produces $BH_4$ presumably because only the former cells do not have an intact pathway for biosynthesis of $BH_4$. Activation of the human cellular immune system is associated with greatly increased formation of the pteridines, neopterin and 7,8-dihydroneopterin and increased neopterin excretion. The increase of neopterin during cell immune response stimulation seems to be nonspecific and secondary phenomenon. On the other hand the investigations have not proved immunomodulatory roles of dihydroneopterin triphosphate (1,7). Also, no immune deficit in children with GTP-cyclohydrolase deficit has not been proven.

High urinary neopterin concentrations are found in patients with viral infections, allograft rejection episodes, and some malignant diseases. In various tumor types high urinary neopterin concentrations are associated with a worse prognosis (19).

## Biochemical disorders of tetrahydrobiopterin ($BH_4$) metabolism

The disorders in $BH_4$ metabolism impair hydroxylation of phenylalanine causing tetrahydrobiopterin-deficient forms of hyperphenylalaninemia.

There are two forms of hyperphenylalaninemia, classic phenylketonuria (typically associated with mental retardation if amino acid phenylalanine is present in the intaken food and nonphenylketonuric hyperphenylalaninemia, non responsible to restriction of phenyalalanine from the diet; this other form is responsive to $BH_4$ (2,3).

$BH_4$ deficiency can be caused by mutation in genes encoding the enzyme involved in its biosynthesis. These inherited enzyme defects are identified through screening program due to existence of evident hyperphenylalaninemia. The mutations are all inherited in an autosomal recessive manner. It is a heterogeneous group of diseases accompanied by the progressive neurological symptoms a cause a deficit of neurotransmitters dopamine and 5-hydroxytryptamine, serotonin (20-25). In the present literature 4 congenital defects of enzymes have been described. The most frequent is the congenital deficit of 6-pyruvoyltetrahydrobiopterin synthase (6-PTS) followed by less frequent GTP-cyclohydrolase (GTP-CH). The deficit of carbinolamine dehydratase (PCD), as well as dihydropteridine reductase (DHPR) has been also established. Clinical manifestations of these enzymes deficits, found in children, are very similar and don't differ from those in classical phenylketonuria (PKU) (7).

The diseases affect either all organs, including the central nervous system, or only the peripheral hepatic phenylalanine hydroxylasing system. The disturbance of brain function such as loss of head control, hypertonia, drooling, swallowing difficulties and myoclonic convulsions develop during three months and is unresponsive to a low-phenylalanine. The exception is in the case of carbinamin dehydratase deficiency; there are no mentioned clinical manifestations except mild hyperphenylalaninemia. Moreover, two forms of $BH_4$ deficiency may occur without hyperphenylalaninemia in infancy; the autosomal dominantly inherited and compound heterozygote form GTP-CH deficiency (Dopa-responsive distonia or Segawa disease) together with an apparent central nervous system - localized form of DHPR deficiency (7).

*6-Pyruvoiltetrahydropterin synthase (6-PTS) deficiency* caracterises with high level of plasma phenylalanine promptly felling and remains normal for 2 days after infusion of $BH_4$ (2.5 mg /kg). A block in biosynthesis of $BH_4$ causes high neopterin levels and no detectable biopterin in urine. /The diagnosis of $BH_4$ deficit or inefficiacy of corresponding enzymes could be established by measuring of neopterin and biopterin in body fluids, especially urine. Neopterin is oxidative product of dihydroneopterin triphosphate, while biopterin is oxidative product of dihydro and tetrahydrobiopterin/.

*GTP-CH deficiency* blocks the beginning of the $BH_4$ synthesis pathway. Neopterin and biopterin levels are both low, and neopterin/biopterin ratio is normal in urine, plasma, and CSF; the high levels of phenylalanine and low levels of neurotransmitter derivatives in body fluids return to the normal values with $BH_4$ replacement (7).

The patients with *carbinolamine dehydratase deficit (PCD)* excrete 7-biopterin by urine.

*Dihydropteridine reductase (DHPR) deficiency* was the first described disorder in $BH_4$ homeostasis. This enzyme deficit has a profound effects on metabolism (Mikaeloff Epileptic disorders, 2000). The patients develop convulsions and other signs of neurological disturbances, starting from the third week of life, inspite of good dietary control of phenylalanine concentration. The patients are deficited in neurotransmitters (dopamine, noradrenalin and serotonin), which synthesis depends on DHPR-dependent tyrosine and tryptophan hydroxylases. They have low level of urinary and cerebrospinal 3-methoxy-4-hydroxy phenylglycol (MHPG) and vanylmandelic acid (VMA), major metabolites of norepinephrine; homovanylinic acid (HVA), major metabolite of dopamine and 5-hydroxyindolacetic acid (5-HIAA)-the metabolite of serotonin. The level of hepatic phenylalanine hydroxylase and $BH_4$ were adequate, but there was no activity of DHPR. It has been proven that the enzyme DHPR keep folates in active tetrahydro form (THF), which is necessary for DNA and RNA synthesis. The other consequence of DHPR inactivity is folate deficit connected to diminish synthesis of proteins (7).

### $BH_4$ and other metabolic disease - perspectives

$BH_4$ is a cofactor which regulates the function of three hydroxylases (for phenylalaline, tryptophan and tyrosine) and therefore the levels of important hormones and neurotransmitters - catecholamines, melanine, serotonine, melatonine. As a cofactor for all three isoenzymes of nitric oxide synthase (NOS), $BH_4$ participates in production not only of nitric oxide (NO), more over hydrogen peroxide ($H_2O_2$) and peroxy-nitrite radical (ONOO-).There are many relationships between $BH_4$ and diabetes mellitus and hypertension (26,27). In patients with the depigmentation disorder vitiligo accumulated hydrogen peroxide is accompanied by high concentration of 6- and 7- biopterin in their epidermis. The investigators of this event suggest that $H_2O_2$ derived from various sources could be a general mechanism in the regulation of all $6BH_4$-dependent processes (28).

The investigation of relationship between polyamine oxidase (PAO), the key regulatory enzyme of polyamine metabolism, generating $H_2O_2$, and $BH_4$ may be of interest for explanation of biochemical function of polyamines; on the other hand the biosynthesis of polyamines, spermine, spermidine and putrescine depend on the amino acids arginine and methionine (29) as S-adenosyl methionine (SAM)(29,30). All these facts suggest possibility of connection (participation of $BH_4$ in polyamine metabolism) between polyamines and $BH_4$ metabolism.

The fact that $BH_4$ synthesis requires the depletion of GTP, nucleoside triphosphate important both in many signaling pathways through Guanine nucleotide regulatory proteins, (G proteins) and or GTP-binding proteins in translation process during the protein synthesis points out many possibilities of $BH_4$ in the mentioned metabolic event in the cells.

Forthcoming investigations will explain the exact biochemical roles of $BH_4$, the chief natural molecule for the future time.

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# BIOHEMIJSKE FUNKCIJE I KLINIČKI ZNAČAJ NEKONJUGOVANIH PTERIDINA

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Kratak sadržaj: *Tetrahidrobiopterin ($BH_4$) i njegovi metaboliti klasifikuju se kao nekonjugovani pteridini ili pterini za razliku od folne kiseline i njenih derivata koji čine grupu konjugovanih pteridina. $BH_4$ nije vitamin za sisare, koji mogu da ga sintetišu. GTPje glavni prekursor atoma u molekulu pterina. Glavni stupanj na putu prevodjenja GTP-a u D-erithro-7, 8-dihidroneopterin trifosfat, je reakcija katalizovana od strane enzima GTP-ciklohidrolaze I (EC 3.5.4.16; GTP-CH). Postoje brojne metabolički značajne funkcije $BH_4$: on je ključni kofaktor u reakcijama hidroksilacije fenilalanina, tirozina i triptofana. Upoznavanje učešća $BH_4$ u regulaciji metabolizma monoaminergičnih neurotransmitera dovelo je do boljeg upoznavanja atipičnih neuroloških simptoma u nekim oblicima "fenilketonuričnе" dece. Kao kofaktor azot oksid sintaze $BH_4$ je ključni metabolit zar fiziološke funkcije kardiovaskularnog sistema. Podaci iz literature ukazuju da deplecija $BH_4$ je ključna u kontroli produkcije NO i vodonik peroksida ($H_2O_2$) pomoću endotelijalne NOS iziforme, i posledičnog formiranja celularno toksičnog peroxinitrita ($ONOO^-$). Medjuodnosi u biosintezi $BH_4$ i guanin nukleotid regulatornih proteina (G proteina) ili GTP-vezujućih proteina koji su uključeni u proces biosinteze proteina potrebno je tek razjasniti. Ideja da sve oksidaze koje koriste molekularni kiseonik i produkuju $H_2O_2$ zahtevaju $BH_4$ jeste veoma interesantna. Ova konstatacija može doprineti boljem upoznavanju aktivnosti poliamin oksidaze (PAO) u regulaciji metabolizma poliamina.*

Ključne reči: *Nekonjugovani pteridini, $BH_4$, GTP-vezujući proteini, poliamini, klinički poremećaji*