Subsystem: Pterin Biosynthesis:
Tetrahydrobiopterin (BH4) biosynthesis and regeneration

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I. Introduction

- Tetrahydrobiopterin (BH4) is a cofactor used in various processes. It has been extensively studied in mammalian systems were BH4 has a well characterized function as a natural cofactor of aromatic amino acid hydroxylases, nitric oxide synthase, and glyceryl ether monooxygenase (for review see: Biochem J, 2000 347: 1-16) The pathway has been characterized and all the three enzymes involved in the pathway (GTPCYHI, PTPS and SPR) crystallized. The pathway has high medical relevance. An alternative path replacing SPR with AR and CR is found in human (Arch Biochem Biophys, 2003 416: 180-7).The cofactor is regenerated by the PCD and DPR enzymes. BH4 is found as glycosidic forms in certain prokaryotes, including cyanobacteria, *Chlorobium tepidum* and the Archaea *Sulfolobus solfataric*us.

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II. Subsystem notes

A subsystem diagram including the list and abbreviations of functional roles and pathway intermediates is provided in Figure 1. A representative section of the subsystem spreadsheet is shown in Figure 2 (modified from the full display available in SEED)..

Enzyme families involved in this subsystem contain an unusually high frequency of paralogs in eukaryotic genomes. This is a substantial impediment for projection of annotations, and our current representation of the eukaryotic variant of this subsystem is limited to the human pathway **(variant 1)**.

In bacteria, a sepiapterin reductase (SPR) has been experimentally verified in *Chlorobium tepidum* (FEMS Microbiol Lett 2005, 242:95-99). It belongs to the vast short-shain dehydrogenase-reductase (SDR) superfamily, a notorious challenge for homology-based annotation. Using a combination of chromosomal clustering and phylogenetic analysis, SPR annotations were expanded over a limited set of organisms (including several cyanobacteria). The absence of an SPR candidate in *Synechocystis*, suggests that it may have an alternative CR/AR pathway. This conjecture is consistent with an observation that *Synechocystis* is one of the few bacterial species containing a homolog of the human AKR1.

A glycosyltranferase BGluT involved in the pathway was experimentally verified in *Synechococcus* PCC7942 (FEBS Lett, 2001 502: 73-8). A candidate for a second glycosyl transferase was tentatively identified in the same chromosomal cluster conserved in many cyanobacteria.

In Pseudomonas, PAH and PCD have been implicated in L-tyrosine metabolism (Proc Natl Acad Sci USA, 1994 91: 1366-70). However, is not obvious that the BH4 pathway is actually present in these organisms as other tetrahydropterin derivatives originating from the folate pathway may be utilized instead (PAH accepts a wide range of tetrahydropteridines *in vitro* – see Biochemistry, 1986 25: 4762-71). It is noteworthy that about two-thirds of bacterial genera have genes encoding PCD homologs, but only a few of those have PAH. Since the only role of PAH is to recycle a pteridine that has served as an electron donor, this observation suggests that there may be a common but unknown pterin-dependent enzyme in bacteria. In general, many aspects of this subsystem in bacteria remain to be elucidated (as reflected in **"0" variant** codes associated with included bacterial genomes).

Figure 1. Subsystem diagram

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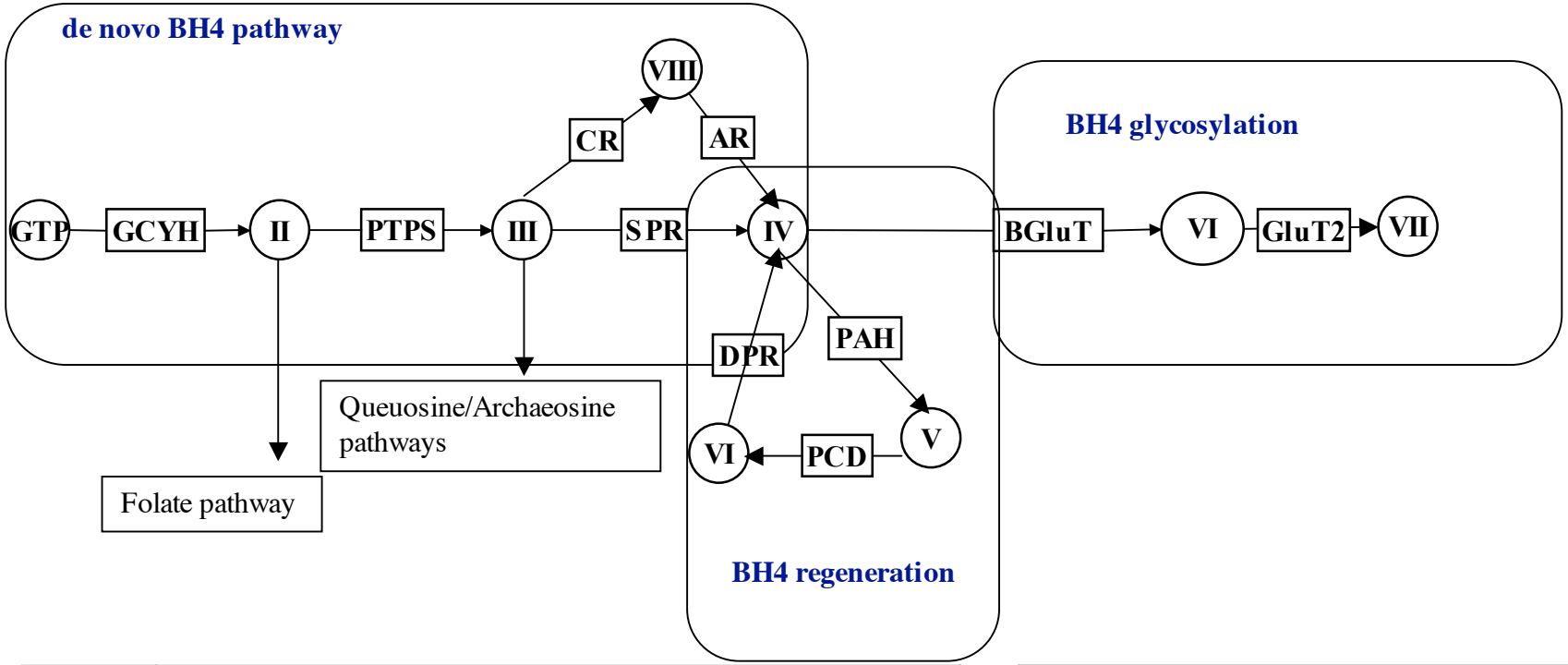
BH4 biosynthesis recycling and regeneration



Abbrev	Functional Role
GCYHI1	GTP cyclohydrolase I (EC 3.5.4.16) type 1
GCYHI2	GTP cyclohydrolase I (EC 3.5.4.16) type 2
PTPS	6-pyruvoyl tetrahydrobiopterin synthase (EC 4.2.3.12)
SPR	Sepiapterin reductase (EC 1.1.1.153)
DPR	Dihydropteridine reductase (EC 1.6.99.7)
PAH	Phenylalanine-4-hydroxylase (EC 1.14.16.1)(among other BH4 dependent enzymes)
PCD	Pterin-4-alpha-carbinolamine dehydratase (EC 4.2.1.96)
BGluT	UDP-glucose:tetrahydrobiopterin glucosyltransferase (EC:2.4.1.-)
GluT2	4-amino-4-deoxy-L-arabinose transferase and related glycosyltransferases of PMT family
CR	Aldo-keto reductase family 1, member C3 (EC 1.1.1.-)
AR	Aldo-keto reductase family 1 member B10 (EC 1.1.1.-)

Abbrev	intermediates
GTP	guanosine ribonucleotide triphosphate
II	7,8-dihydroneopterin triphosphate
PTP	6-pyruvoyltetrahydropterin
IV	5,6,7,8-tetrahydrobiopterin
V	Tetrahydropterin-4a-carbinolamine
VI	q-Dihydrobiopterin
VI	BH4-glucoside
VII	Cyanopterin

Figure 2. Subsystem sprteadsheet (fragment)

Subsystem: Pterin Biosynthesis

		BH4 biosynthesis			BH4 synthesis		BH4 recycling or aromatic aa catabolism			BH4 Glycosylation	
Organism	Variant Code	GCYHI 1	PTPS	SPR	AKR1B1	AKR1C3	DPR	PAH	PCD	BGluT	GluT2
Chlorobium tepidum TLS [B]	0	770	771	603					340	?	361
Gloeobacter violaceus PCC 7421 [B]	0	1580	3579	?					926	1887	3582
Synechococcus elongatus PCC 7942 [B]	0	919	515	918						1229	1546, 157
Synechococcus sp. WH 8102 [B]	0	1727	1499, 2194	1728						1875	1874, 2213, 2220
Synechocystis sp. PCC 6803 [B]	0	2437	2581	?	1823					1757	
Nostoc sp. PCC 7120 [B]	0	5028, 5594	391, 4861	5593						3027	3177
Prochlorococcus marinus subsp. marinus str. CCMP1375 [B]	0	1576, 536	127, 582	534						1291	1290
Pseudomonas aeruginosa PAO1 [B]	0	1675, 3438	2666				?	873	872		
Pseudomonas putida KT2440 [B]	0	1808, 2490	2320				2410	4431	4432		
Homo sapiens [E]	1	398	549	3153	10919, 26578, 27629	3709	552	510	1348, 513		