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Review

PLP-dependent enzymes as potential drug targets for protozoan diseases ☆

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ABSTRACT

The chemical properties of the B_6 vitamers are uniquely suited for wide use as cofactors in essential reactions, such as decarboxylations and transaminations. This review addresses current efforts to explore vitamin B_6 dependent enzymatic reactions as drug targets. Several current targets are described that are found amongst these enzymes. The focus is set on diseases caused by protozoan parasites. Comparison across a range of these organisms allows insight into the distribution of potential targets, many of which may be of interest in the development of broad range anti-protozoan drugs. This article is part of a Special Issue entitled: Pyridoxal Phosphate Enzymology.

1. Introduction

Protozoa synthesize vitamin B_6 in the form of PLP from pentose and triose phosphate substrates, utilising *in situ* generated ammonia as a nitrogen source [1]. Vitamin B_6 salvage pathways are also known, and these involve uptake of unphosphorylated precursors with subsequent phosphorylation inside the cells [1]. Drug development based on enzymatic targets in these pathways has recently been discussed for protozoan parasites [2,3].

In this review, we have analyzed PLP-dependent enzymes from 15 protozoan parasites. From the subphylum Mastigophora (Flagellata) the orders Kinetoplastida with *Leishmania major*, *Trypanosoma brucei* and *Trypanosoma cruzi* as representatives, Diplomonadida with *Giardia lamblia* as a member and Trichomonadida with *Trichomonas vaginalis* as associate were selected. The subphylum Sarcodina (Amoebae) is represented by *Entamoeba histolytica*. The phylum Apicomplexa (Sporozoa) which harbours parasites of veterinary importance as well as human pathogens is represented by the following parasites: *Plasmodium falciparum* and *vivax* from the order Haemosporida, *Babesia bigemina*, *Theileria annulata* and *Theileria parva* from the Piroplasmida, and *Eimeria tenella*, *Cryptosporidium parvum*, *Cryptosporidium hominis* and *Toxoplasma gondii* from the order Eucoccidiorida. The genomes of these organisms were screened with the metatiger software (http://www.bioinformatics.leeds.ac.uk/metatiger/), using the cofactor search option with the query string "PLP" and by manual inspection of EuPathDB (http://eupathdb.org/eupathdb/) and GeneDB (http://www.genedb.org/) for the EC numbers and gene product names of PLP-dependent proteins [4] (see Supplement, Table S1). For further information the genome databases of the individual parasites (http://tritrypdb.org/tritrypdb/, http://amoebadb.org/amoeba/, http://giardiadb.org/giardiadb/, http://trichdb.org/trichdb/, http://plasmodb.org/plasmo/, http://beta.piroplasmadb.org/piro.b10/, http://cryptodb.org/cryptodb/, http://toxodb.org/toxo/) were screened except for *E. tenella*, which was accessed via http://www.genedb.org/Homepage/Etenella, since the genome data is not available on http://eupathdb.org/eupathdb/. As the EC number search for *E. tenella* did not yield any results, the respective database was solely searched for the gene product names. In total, 44 PLP-dependent enzymes were identified (Table 1). The individual gene IDs are provided in Supplemental Fig. 1 and are referring to the gene IDs of the parasite-specific databases, which are listed above. The only exception is *E. tenella*, where the GeneDB ID has been provided.

PLP-dependent enzymes have been classified into seven structural superfamilies named according to their prototype members [5]. Grishin et al. [6] were first to establish this structural classification, which was later refined by Percudani and Peracchi [4]. The prototype superfamilies have developed approximately 1.5 to 1.0 billion years ago [7], well before the three biological kingdoms came into existence. Today, we find a wide functional variety within each of the seven superfamilies. The largest of these families is the aspartate aminotransaminase family (fold-type I), consisting of aminotransferases, decarboxylases as well as of enzymes that catalyze α-, β- or γ-eliminations. The tryptophan synthase β-family (fold-type II) primarily contains enzymes catalyzing

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Table 1
Protozoan PLP-dependent enzymes.

	Phylum	Sarcomastigophora						Apicomplexa						
	Order	Kinetoplastida			Diplomonadida	Trichomonadida	Amoebida	Haemosporida		Piroplasmida		Eucoccidiorida		
	Species	Lm	Tb	Tc	Gl	Tv	Eh	Pf	Pv	Bb	Ta/Tp	Et	Cp/Ch	Tg
1	Glycine dehydrogenase EC1.4.4.2	+ [66]	+	+	–	–	–	–	–	–	–	–	–	–
2	Glycine hydroxymethyltransferase (serine HMT) EC 2.1.2.1	+	–	+ [67]	–	+	–	+ [50, 68, 69]	+	+	+/+	+	+/+	+/+
3	Glycine C-acetyltransferase EC2.3.1.29	–	+ [70]	+	–	–	–	–	–	–	–	–	–/–	–
4	5-aminolevulinic acid synthase EC2.3.1.37	–	–	–	–	–	–	+ [71] [a]	+	–	–	+	–	+/+
5	8-amino-7-oxononanoate synthase EC2.3.1.47	–	–	–	–	–	–	–	–	–	–	–	+	–
6	Serine C-palmitoyltranserase (CW) EC2.3.1.50	+ [72]	+	+	+	+	+	+ [a]	+	–	–	+	–	+/+
7	Phosphorylase EC2.4.1.1	–	–	–	+	+	+	-[73]	–	–	–	+	+/+	+/+
8	Cysteine synthase/(O(3)-acetyl-L-serine acetate-lyase) EC2.5.1.47	+ [49]	–	+	–	+ [46]	+	–	–	–	–	+	–	+
9	Aspartate transaminase EC2.6.1.1	+	+	+	+	+	+	+ [14] [a]	+	+	+/+	+	–	+/+
10	Alanine transaminase EC2.6.1.2	+	+	+	+	+ [74]	+	–	–	–	–	+	–	+/+
11	Cysteine amino transferase EC2.6.1.3	+	–	–	–	–	–	–	–	–	–	–	–	–
12	Tyrosine transaminase EC2.6.1.5	+	–	+ [75, 76]	–	+	–	–	–	–	–	–	–	–
13	Kynurenine–oxoglutarate transaminase EC2.6.1.7	–	+	–	–	–	–	–	–	–	–	–	–	–
14	Ornithine–oxo-acid transaminase EC2.6.1.13	–	–	–	–	–	–	+ [77] [a]	+	–	–	+	–	+/+
15	Branched-chain-amino-acid transaminase EC2.6.1.42	+	+	–	+	+	+	+ [a]	+	–	–	+	–	+/+
16	Alanine-glyoxalate transamininase EC2.6.1.44	+ [78]	–	+	–	–	–	–	–	–	–	–	–	–
17	Glutaminase–scyllo-inositol transaminase EC2.6.1.50	–	–	–	–	–	–	–	–	–	–	+	–	–
18	Serine-pyruvate transaminase EC2.6.1.51	–	–	–	+	–	–	–	–	–	–	+	–	+/+
19	Phosphoserine transaminase EC2.6.1.52	–	–	–	–	+ [46]	+	–	–	–	–	+	–	+/+
20	Aromatic amino acid transaminase EC2.6.1.57	–	–	–	–	–	–	–	–	–	–	–	–	+