

Treatment of Human Porphyria's with Glucose and Antioxidants is Now Best Understood

Mazzetti MB*

Laboratorio de Disturbios Metabólicos por Xenobióticos, Salud Humana y Medio Ambiente, Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, Pab II, 4to Piso, C1428EGA Ciudad Autónoma de Buenos Aires, Argentina

Description

Porphyrias are hereditary disorders caused by the de-regulation of the heme pathway due to a deficiency in some of its enzymes, which lead to lower heme formation. This deficiency triggers the induction of the regulatory enzyme ALA-synthase (ALA-S) [1].

Acute porphyrias are the most dangerous since they are life-threatening and can be fatal. They are biochemically characterized by the accumulation of heme precursors such as ALA, which generates reactive oxygen species (ROS) thus promoting oxidative stress.

Porphyrinogenic drug 2-allyl-2-isopropylacetamide (AIA) increases the destruction of liver heme, particularly cytochrome P-450 [2], whereas porphyrinogenic drug 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) is a potent depletor of hepatic heme due to its combined property of destroying heme and inhibiting heme synthesis [3]. AIA/DDC treatment results in acute deficiency of heme, marked de-repression of ALA-S and, consequently, exacerbated production of ALA and other heme precursors in the liver [4]. This combined treatment has been reported to induce an experimental porphyria resembling quite accurately acute variegate porphyria in rats [4]. Accumulated ALA has been associated with iron-mediated oxidative damage to biomolecules and cell structures [5] through reactive oxygen species (ROS) generation [6]. ROS are able to oxidize nucleic acids, proteins, lipids, or carbohydrates, inactivating key cellular functions [7]. It has been demonstrated that AIA/DDC treatment promotes an oxidative environment with ROS increases [4] (Figure 1).

Glucose administration is known to have beneficial effects on acute porphyria patients significantly improving their clinical and biochemical condition [1]. In animal models, the prevention of acute experimental porphyria through high carbohydrate and/or protein intake [8] is an example of the effect of glucose on ALA-S, with carbohydrates preventing the induction of this heme- pathway regulatory enzyme [9].

On the other hand, it has been reported that AIA/DDC treatment promotes gluconeogenic and glycogenolytic blockages leading to reduced glucose availability in hepatocytes. In this respect, hepatic phosphoenol pyruvate carboxykinase and glycogen phosphorylase activities were found impaired in this rat experimental type of porphyria [4,10].

The pentose phosphate (PP)-pathway is primarily an anabolic pathway that uses the 6 carbon atoms from glucose to generate 5 carbon sugars and reducing equivalents. However, this pathway does oxidize glucose and, under certain conditions, can completely oxidize glucose to CO₂ and water. In fact, 30% of glucose oxidation in the liver occurs via the pentose pathway. Glucose-6-phosphate dehydrogenase (G6PD, EC1.1.1.49) is the regulatory enzyme of the (PP)-pathway; it supplies cell riboses for DNA and RNA syntheses [11]. However, its main function is the production of NADPH, the major cytoplasmic reducing component. It has been shown that G6PD function is essential in the defense against oxidative stress-dependent NADPH [12]. The maintenance of the NADPH pool regulates the levels of

reduced glutathione (GSH) which, in turn, is in charge of removing very harmful compounds such as peroxides from cells. GSH is in fact an antioxidant, and prevents damage to important cellular components caused by reactive oxygen species such as free radicals and peroxides [13]. It reduces disulfide bonds formed within cytoplasmic proteins to cysteines by serving as an electron donor. In the process, glutathione is converted to oxidized form glutathione disulfide (GSSG). Glutathione is found almost exclusively in its reduced form, since glutathione reductase (GR) (EC 1.8.1.7), the enzyme that reverts it from its oxidized form, is constitutively active and inducible [14], and is thus a critical enzyme to maintain proper redox status. GR is a FAD-containing enzyme that catalyzes the NADP-dependent reduction of GSSG to GSH. Other GSH enzymes are glutathione peroxidase (GPx) (EC 1.11.1.9) and glutathione S-transferase (EC 2.5.1.18) (GST).

The GPx are a selenium-containing family of enzymes that use GSH to scavenge peroxides in the process of converting GSH to GSSG, thus protecting tissues from oxidative damage. GPx1 is the most abundant form and is expressed in all cell types whose preferred substrate is hydrogen peroxide.

The GST family use GSH in conjugation reactions to bind and remove toxic chemicals, and harmful compounds, aiding in detoxification and forming less reactive substances. This makes GSTs the most important enzymes in chemical defense [15]. GST isoenzymes are designated cytosolic, microsomal and mitochondrial transferases [16]. GSTs are up-regulated by xenobiotics, drugs, cytokines, and endotoxin [16], and at least 100 chemicals have been identified as GST inducers [15]. On the other hand, hematin, bilirubin, biliverdin, biliary acids and halogenated compounds, among others, have been found to inhibit hepatic GST [17,18].

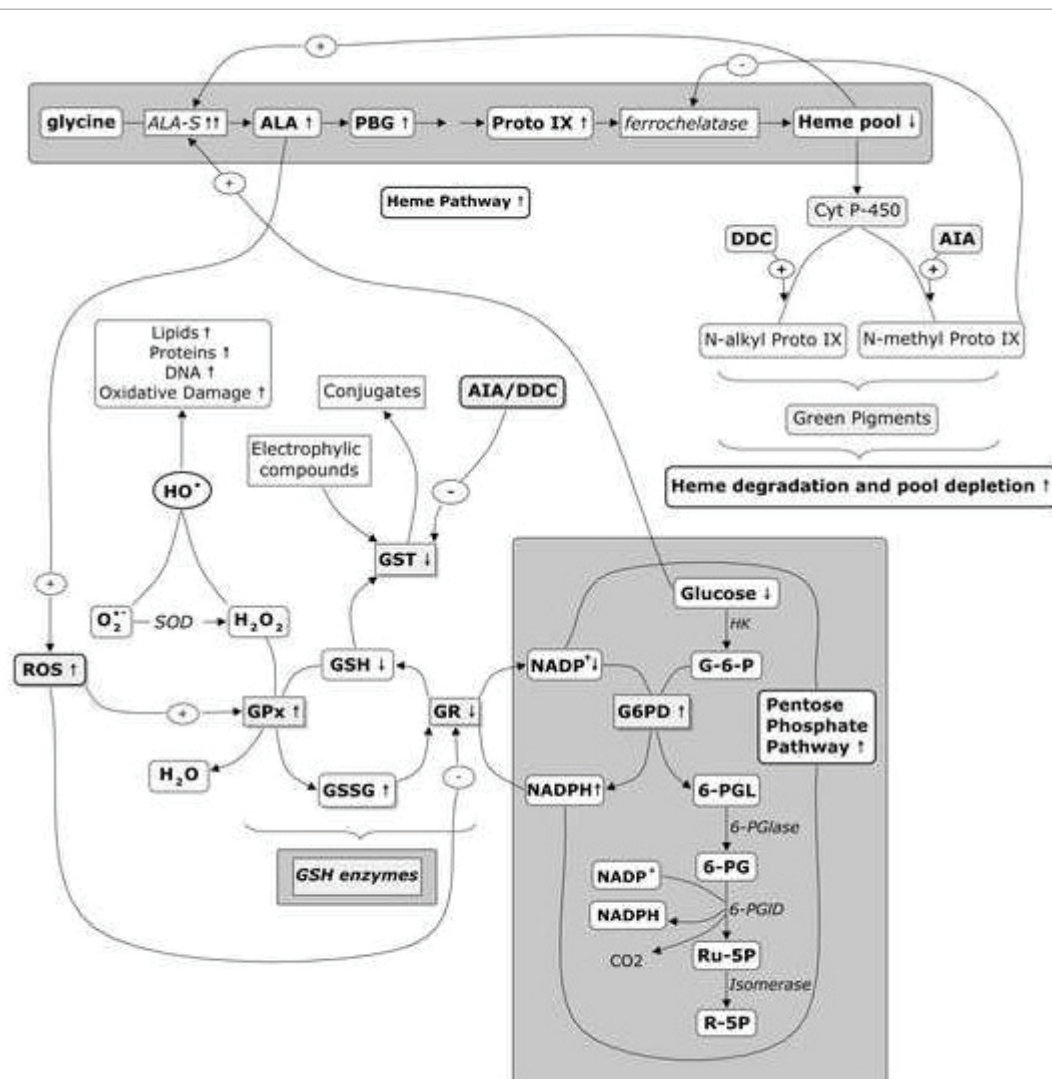
Taking into account that 1) AIA/DDC treatment model of acute porphyria produces oxidative stress with increased ROS production, 2) AIA/DDC treatment promotes gluconeogenic and glycogenolytic blockages leading to lower glucose availability in hepatocytes, and 3) glucose plays a key role in the regulation of the heme pathway, as well as in the treatment of human and experimental porphyrias, it seems interesting to report how the AIA/DDC porphyria model impairs

***Corresponding authors:** Dr. Marta Blanca Mazzetti, Laboratorio de Disturbios Metabólicos por Xenobióticos, Salud Humana y Medio Ambiente, Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, Pab II, 4to Piso, C1428EGA Ciudad Autónoma de Buenos Aires, Argentina, Fax: 54 11 4576 3342; E-mail: mazzetti@qb.fcen.uba.ar

Received November 03, 2016; **Accepted** November 24, 2016; **Published** November 28, 2016

Citation: Mazzetti MB (2016) Treatment of Human Porphyria's with Glucose and Antioxidants is Now Best Understood. J Mol Genet Med 10: 233 doi:[10.4172/1747-0862.1000233](https://doi.org/10.4172/1747-0862.1000233)

Copyright: © 2016 Mazzetti MB. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited



Abbreviations: AIA: 2-Allyl-2-Isopropylacetamide; ALA: 5-Aminolevulinic Acid; ALA-S: ALA-Synthase; DDC: 3,5-Diethoxycarbonyl-1,4-Dihydrocollidine; Cyt P-450: Cytochrome P-450; GSH: Reduced Glutathione; GSSG: Glutathione Disulfide; G-6-P: Glucose-6-Phosphate; G6PD: Glucose-6-Phosphate Dehydrogenase; Gpx: Glutathione Peroxidase; GR: Glutathione Reductase; GST: Glutathione S-Transferase; GSH Enzymes: Enzymes of Glutathione Metabolism; HK: Hexokinase; NADP⁺: Nicotinamide Adenine Dinucleotide Phosphate; NADPH: Reduced NADP⁺; PBG: Porphobilinogen; 6-PG: 6-Phosphogluconate; 6-PGL: 6-Phosphogluconolactone; 6-PGLase: 6-Phosphogluconolactonase; 6-PGLD: 6-Phosphogluconate Dehydrogenase; Proto IX: Protoporphyrin IX; Ru-5P: Ribulose-5-Phosphate; R-5-P: Ribose-5-Phosphate; ROS: Reactive Oxygen Species; SOD: Superoxide Dismutase.

Figure 1: Scheme on the effect of AIA/DDC treatment on different metabolic routes (pentose phosphate pathway, heme pathway, ROS generation, GSH metabolism) leading to oxidative stress, toxic response Glucose decrease and porphyria exacerbation.

the PP-pathway, which consumes glucose and generates NADPH involved in redox reactions, as well as comment the impact produced on GSH enzymes GR, GPx and GST, responsible for maintaining the status of GSH, the major endogenous antioxidant produced by cells. Our group detected a disruption in glutathione metabolism and PP-pathway, lowering GSH/GSSG ratio 4-fold (Figure 1). These effects are a consequence of both decreased activity of GR, responsible for GSH formation, and increased activity of GPx, which oxidizes GSH to GSSG [19]. Thus, it was attributed to reactive oxygen species generation elicited by the porphyrinogenic treatment. Therefore, G6PD stimulation decreased hepatic glucose level and consequently modulate the porphyria exacerbating it. This decrease exerts a stimulator effect on 5-aminolevulinic acid synthase, the regulatory enzyme of the heme pathway; this stimulation would add to that of drug induced-heme

depletion. From these findings, treatment of human porphyrias with glucose and antioxidants is now best understood.

Conflict of Interest

The author declares that there are no conflicts of interest.

Acknowledgement

This work is supported by grants from the Universidad de Buenos Aires (UBACyT).

References

1. Kappas A, Sassa S, Galbraith RA, Nordmann Y (1995) The porphyrias. In: Metabolic and molecular basis of inherited disease, McGraw-Hill, New York, USA.
2. Smith AG, De Matteis F (1980) Drugs and the hepatic porphyrias. Clin Haematol 9: 399-425.

3. Marks GS, McCluskey SA, Mackie JE, Riddick DS, James CA (1988) Disruption of hepatic heme biosynthesis after interaction of xenobiotics with cytochrome P-450. *FASEB J* 2: 2774-783.
4. Lelli SM, San Martin de Viale LC, Mazzetti MB (1995) Response of glucose metabolism enzymes in an acute porphyria model. Role of reactive oxygen species. *Toxicology* 216: 49-58.
5. Rocha ME, Dutra F, Bandy B, Baldini RL, Gomes SL, et al. (2003) Oxidative damage to ferritin by 5-aminolevulinic acid. *Arch. Biochem Biophys* 409: 349-356.
6. Monteiro HP, Abdalla DSP, Augusto O, Bechara EJM (1989) Free radical generation during delta-aminolevulinic acid autooxidation: induction by hemoglobin and connections with porphyriopathies. *Arch Biochem Biophys* 271: 206-216.
7. Halliwell B, Gutteridge JMC (1999) *Free radicals in biology and medicine*. (3rd edn), Oxford University Press, London, UK.
8. Rose JA, Hellman ES, Tschudy DP (1961) Effect on diet on induction of experimental porphyria. *Metabolism* 10: 514-521.
9. Tschudy DP, Welland FH, Collins A, Hunter G Jr. (1954) The effect of carbohydrate feeding on the induction of delta-aminolevulinic acid synthetase. *Metabolism*;13: 396-406.
10. Matkovic LB, D'Andrea F, Fornes D, San Martín de Viale LC, Mazzetti MB (2011) How porphyrinogenic drugs modeling acute porphyria impair the hormonal status that regulates glucose metabolism. Their relevance in the onset of this disease. *Toxicology* 290: 22-30.
11. Berg JM, Stryer L, Tymoczko JL (2007) *Biochemistry*, (6th edn), Freeman WH and Co, New York, USA.
12. Spolarics Z (1998) Endotoxemia, pentose cycle, and the oxidant/antioxidant balance in the hepatic sinusoid. *J Leukoc Biol* 63: 534-541.
13. Pompella A, Visvikis A, Paolicchi A, De Tata. V, Casini AF (2003) The changing faces of glutathione, a cellular protagonist. *Biochem Pharmacol* 66: 1499-1503.
14. Pastore A, Piemonte F, Locatelli M, Lo Russo A, Gaeta LM, et al. (2001) Determination of blood total, reduced and oxidized glutathione in pediatric subjects. *Clin Chem* 47: 1467-1469.
15. Hayes JD, Pulford DJ (1995) The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. *Crit Rev Biochem Mol Biol* 30: 445-600.
16. Higgins LG, Hayes JD (2011) Mechanisms of induction of cytosolic and microsomal glutathione transferase (GST) genes by xenobiotics and pro-inflammatory agents. *Drug Metab Rev* 43: 92-137.
17. Ahmad H, Singh S, Awasthi YC (1991) Inhibition of bovine lens glutathione S-transferases by hematin, bilirubin and bromosulphophthalein. *Lens Eye Toxic Res* 8: 431-440.
18. Aniya Y, Anders MW (1985) Alteration of hepatic glutathione S-transferases and release into serum after treatment with bromobenzene, carbon tetrachloride, or N-nitrosodimethylamine. *Biochem Pharmacol* 34: 4239-4244.
19. Faut M, Paiz A, de Viale LCSM, Mazzetti MB (2013) Alterations of the redox state, pentose pathway and glutathione metabolism in an acute porphyria model. Their impact on heme pathway. *Exp Biol Med* 238: 133-143.

Citation: Mazzetti MB (2016) Treatment of Human Porphyria's with Glucose and Antioxidants is Now Best Understood. J Mol Genet Med 10: 233
doi:10.4172/1747-0862.1000233

OMICS International: Open Access Publication Benefits & Features

Unique features:

- Increased global visibility of articles through worldwide distribution and indexing
- Showcasing recent research output in a timely and updated manner
- Special issues on the current trends of scientific research

Special features:

- 700+ Open Access Journals
- 50,000+ editorial team
- Rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at major indexing services
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: <http://www.omicsonline.org/submission/>