

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

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### 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 CO<sub>2</sub> 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].

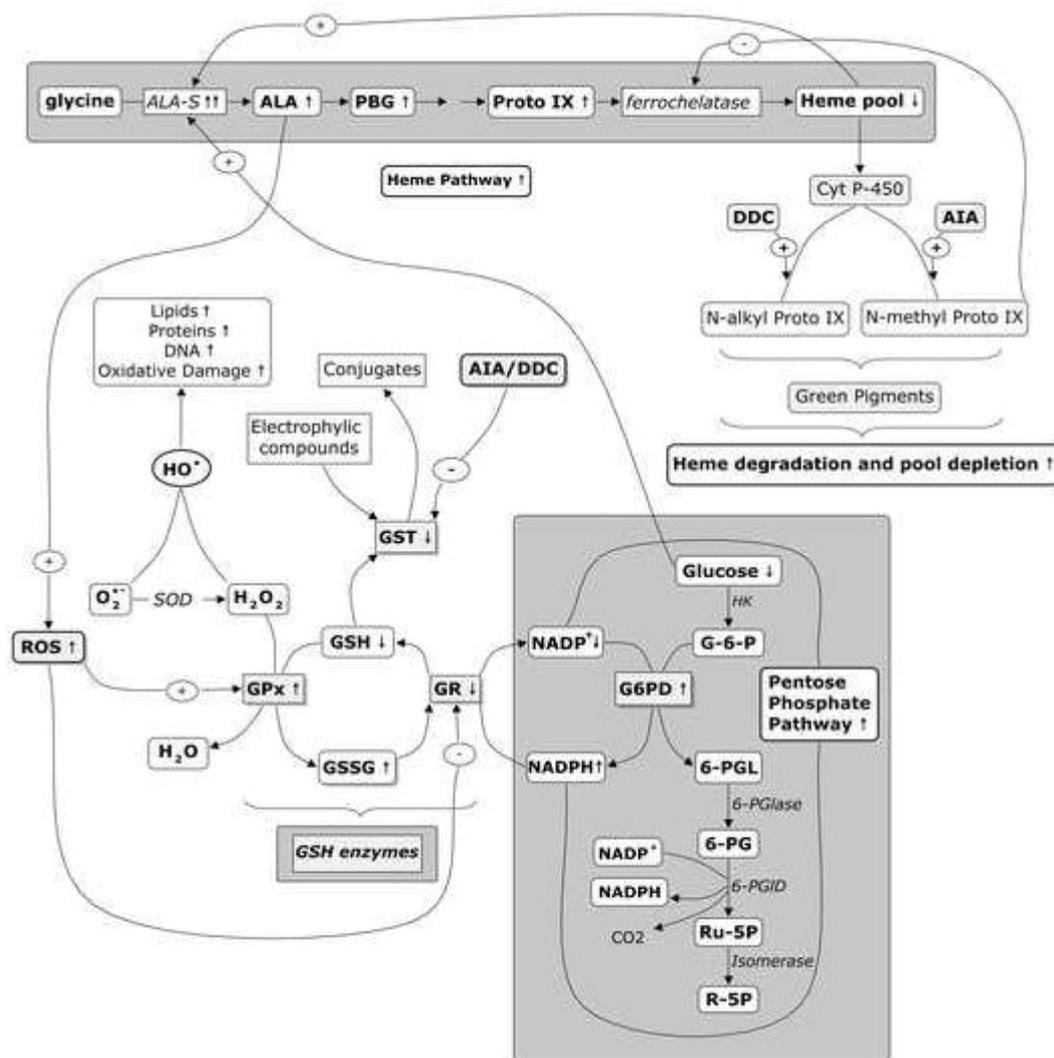
Taking into account that 1) AIA/DDC treatment model of acute porphyria produces oxidative stress with increased ROS production, 2) AIA/DDC treatment promotes gluconeogenic and glycogenolytic blockages leading to lower glucose availability in hepatocytes, and 3) glucose plays a key role in the regulation 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

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**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<sup>+</sup>: Nicotinamide Adenine Dinucleotide Phosphate; NADPH: Reduced NADP<sup>+</sup>; 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.

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