Acute Hepatic Porphyrias

Subjects: Medicine, General & Internal

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Porphyrias are a group of congenital and acquired diseases caused by an enzymatic impairment in the biosynthesis of heme. Depending on the specific enzyme involved, different types of porphyrias (i.e., chronic vs. acute, cutaneous vs. neurovisceral, hepatic vs. erythropoietic) are described, with different clinical presentations. Acute hepatic porphyrias (AHPs) are characterized by life-threatening acute neuro-visceral crises (acute porphyric attacks, APAs), featuring a wide range of neuropathic (central, peripheral, autonomic) manifestations.

Keywords: porphyria ; acute hepatic porphyrias ; aminolevulinic acid ; heme ; neuronal damage ; porphobilinogen ; nitric oxide ; tryptophan dioxygenase

1. Introduction

Porphyrias are a group of congenital and acquired diseases characterized by an impairment of the heme biosynthetic pathway [1]. Depending on the distinct enzyme deficiency and the tissue-specific isoform involved, different kinds of porphyria are described, the main distinction being made between cutaneous (or non-acute) porphyrias (congenital erythropoietic porphyria, porphyria cutanea tarda, hepato-erythropoietic porphyria, and X-linked/erythropoietic protoporphyria), mainly featuring a clinical picture of cutaneous phototoxicity, and acute hepatic porphyrias (AHPs). The latter comprise ALA dehydratase deficiency porphyria (AlaD-P), acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP). Both AlaD-P and AIP present only with acute neurovisceral manifestations, whereas HCP and PV display neurovisceral as well as subacute photosensitivity symptoms [2].

The exact mechanism underlying the neurologic impairment in AHP is still a matter of debate. In recent decades, the majority of authors have focused on the occurrences of direct ALA neurotoxicity, neurologic damage following heme depletion, and a few others. In fact, the pathway leading to the biosynthesis of heme is inscribed into a complex network of interactions that also includes some of the most fundamental processes of basal metabolism. Therefore, a disruption in any of the steps of this pathway is likely to interfere in a pleiotropic fashion with the viability of cells and tissues, thus giving rise to multiple possible mechanisms of pathogenesis (**Figure 1**, created with BioRender.com).

2. *δ*-Aminolevulinic Acid Toxicity

2.1. Mechanisms of Transport and Uptake of δ-ALA in the CNS

When considering the hypothesis of a direct damaging effect of ALA to the brain, some issues arise regarding the possibility of ALA to effectively reach neurotoxic concentrations in the CNS under physiologic conditions.

When incubated with high ALA concentrations (4.0 mM), rat cerebral cortex particles accumulate ALA intracellularly and ALAD activity is enhanced, while HMBS acts as a secondary control step, leading to a build-up of PBG [3][4]. More recently, in mice receiving ALA intraperitoneally, ALA accumulation in the encephalon was demonstrated, together with a plethora of effects on brain metabolism (a reduction of brain ALAS mRNA levels, an increase in cerebellar and hippocampal heme oxygenase activity, an increase in acetylcholinesterase activity, and alterations in factors involved in the management of oxidative stress) [5].

In neonatal rat astrocytes, PEPT2 is likely to be the main transporter of ALA; dipeptides, *α*-amino-containing cephalosporins, and a less acidic pH all negatively affect its transport rate [6]. Moreover, PEPT2 expression in astrocytes appears to decrease with age [7].

Following ALA administration, PEPT2-deficient mice showed substantially lower ALA concentrations in the choroid plexus, cerebral cortex, kidney, eye, blood, and plasma (suggestive of a greater renal clearance), but a five-fold greater concentration in CSF, reaching an eight-fold greater CSF/blood concentration ratio. PEPT2 null mice also displayed a

much higher level of susceptibility to ALA toxicity and developed neuromuscular dysfunction following ALA chronic administration; notably, in this study, ALA plasma levels, calculated as the area under the curve, were comparable to those observed in porphyric patients during APAs [8].

In a population of AIP patients, homozygous carriers of a PEPT2 variant with a higher affinity for ALA (PEPT2*1*1) were independently associated with worse renal function and a more severe annual decrease in eGFR, compared to heterozygous or homozygous carriers of a variant with lower affinity (PEPT2*1*2 and PEPT2*2*2) [9]. Conversely, the presence of the PEPT2*2*2 variant was associated with poorer motor dexterity and working memory in children, in the context of low-level lead exposure [10]. Following these pieces of evidence, it has been conjectured that PEPT2 polymorphisms as well as (reversible) functional impairment may act as a modifying factor in defining the penetrance of the AHP phenotype, or even the timing of porphyric attacks [8].

It should be noted that ALA is a substrate for uptake by members of the neurotransmitter sodium and chloride dependent transporter family, whose substrate specificity is, normally, suited to GABA or GABA-like substances such as taurine and β-alanine [11]. In vitro evidence of ALA uptake was found for the transporters SLC6A6, SLC6A13 (whose affinity for ALA was suggested also through homology modeling [12]), possibly SLC6A8 [13], SLC15A1, and SLC36A1 [14]. The latter, in particular, is present in most parts of the human gastroenteric tract, peaking in expression in the small bowel; its mRNA is also detected in the blood-nerve barrier transcriptome [15][16]. These findings, perhaps, should be kept in mind when one thinks of the heightened levels of ALA detected in the peripheral, compared to the central, nervous system [17][18], or of the spasmodic effect exerted by ALA on rat small-bowel preparations [19].

2.2. Endogenous Production of δ-ALA in the CNS

In principle, in the presence of an enzyme dysfunction in heme biosynthesis, rather than being obtained from the bloodstream, ALA could also be endogenously overproduced by the induction of neuronal (or glial) ALA synthase. Objections against this argument have been posited due to the evidence that liver transplantation (LT) is curative in AHPs [20], with most patients who undergo LT also showing a significant improvement in chronic neurological symptoms. Conversely, it has been reported that patients who received liver grafts from AHP donors within “domino” procedures began to suffer from APAs [21]. Nonetheless, several studies have been conducted to ascertain the possibility of an endogenous brain production of ALA.

In mice, brain mitochondrial ALAS activity is very low at birth, it reaches a peak at about 15 days and then declines steadily during the first 12 months of age [22][23]. In vivo, it seems to be unaffected by fasting, ethanol, AIA, DDC, or barbiturates [22][24][25], whereas it decreases after the administration of cycloheximide or large doses of ALA, or its methyl ester [23]. In fact, brain ALAS mRNA levels in mice were shown to diminish following a chronic or acute intraperitoneal administration of ALA [5]. Notably, injected hematin and $CoCl_2$ are not taken up by the brain in vivo and do not affect brain ALAS activity, contrary to the liver isoform [23]. Brain ALAS requires a much lower glycine concentration to reach maximum activity compared to liver, adrenal mitochondrial or heart mitochondrial isoforms [22], but its activity was found to be only 20% compared to the liver isoform. This should still suffice to support the brain’s own requirement for synthesis and turnover of its hemoproteins [23].

Intriguingly, homozygous *Hmbs* knock-in mice show markedly elevated concentrations of ALA and PBG in the whole CNS (i.e., cerebrum, cerebellum, upper brain stem, and lower brain stem), including the spinal cord, and in the CSF [26]. Differently from T1/T2 mice, *Hmbs* knock-in mice do not show an immediate porphyric biochemical response to porphyrinogenic stimuli. However, they develop a severe neuropathy which closely resembles homozygous dominant acute intermittent porphyria, thus reinforcing the hypothesis of direct neurotoxicity exerted by locally produced ALA (and possibly PBG) [26].

2.3. Oxidative Damage, Mitochondrial Alterations and Effects on Iron Homeostasis

From a biochemical perspective, ALA undergoes a phosphate-catalyzed auto-enolization and becomes an oxidizing agent, reacting with iron and O_2 to produce superoxide anion ($O_2\cdot$), $HO\cdot$ radical, and ALA radical ($ALA\cdot$); the latter, in turn, reduces iron and yields the oxidant species dioxovaleric acid (DOVA), by reacting with oxygen [27][28].

Oxidative damage is the main mechanism by which ALA is deemed to cause mitochondrial dysfunction. In vitro, ALA induces mitochondrial swelling and the loss of transmembrane potential [29], possibly due to ROS-driven thiol cross-linking, which may lead to the aggregation of giant pore-like proteins [30]. Interestingly, calcium chelators and (only in the initial phases) catalase and dithiothreitol were able to restore transmembrane potential [29][30]. In addition, in ALA-treated HepG2 cells, an increased expression of mitochondrial biogenesis-related factors and mitochondrial network disruption was observed [31]. Likewise, ALA treatment was shown to alter mitochondrial polarity in rat Schwann cells [32]. ALA-

induced lipid peroxidation has also been observed in vitro in rat astrocytes [33], rat Schwann cells [32] and, notably, in cardiolipin-rich liposomes, with a significant increase in their permeability. More specifically, phosphatidylcholine and cardiolipin (a major component of inner mitochondrial membranes) seem to be particularly susceptible to ALA-driven oxidative damage, even when ALA concentrations are in the micromolar range [28]; this has been proposed as an alternative slow-acting (i.e., with a time scale of hours) mechanism contributing to mitochondrial damage [28].

The high susceptibility of myelin-producing cells to oxidation could also play a pathogenic role. It has been shown that rat Schwann cells cultures, when incubated with ALA, suffer a dose-dependent reduction of proteins involved both in the initial stages of myelin formation, as well as in myelin sheath maintenance; decreased levels of sphingomyelins, phosphatidylcholines, and lysophosphatidylcholines were measured accordingly. At the same time, increased levels of carbonylated proteins and peroxidated lipids were detected, suggesting the activation of oxidative events [32].

ALA-driven oxidation is also supposed to exert a disruptive effect on iron homeostasis. Incubation with ALA alters the secondary and tertiary structure of apoferritin (possibly due to selective oxidative damage in tryptophan and cysteine moieties) and impairs its iron uptake ability (which is dependent on L subunits), while keeping its ferroxidase activity intact (dependent on H subunits) [27]. Additionally, ALA-induced iron release from ferritin has been observed in vitro [34]. In previously fasted succinyl acetone methyl ester (SAME)-treated rats, significant ALA-driven increases of total non-heme iron, lipid peroxidation, and of the antioxidant copper zinc superoxide dismutase (CuZnSOD) activity were detected in the brain [35].

Similar results were obtained by intraperitoneal injections of ALA, which caused an increase in total non-heme iron and ferritin in the cortex, in ferritin content in the striatum, in CuZnSOD activity in brain homogenates, lipid peroxidation and protein carbonylation in synaptic membrane preparations of total brain tissue, and in calcium uptake by cortical synaptosomes [36].

The iron regulatory protein 1 (IRP1) is a post-transcriptional regulator that binds to specific mRNA stem-loop structures known as iron-responsive elements (IRE); IREs are present in the mRNA untranslated regions (UTRs) of several proteins pivotal to iron homeostasis. It is therefore worth noting that incubation with ALA or SAME leads to an increased activity of IRP1, which is preventable by the addition of the cell-permeable antioxidant N-acetylcysteine (but not extracellular-acting catalase or superoxide dismutase) [37]. The authors of this study conclude that intracellular ALA should be numbered amongst the co-sensors in the regulation of iron homeostasis.

2.4. Neurotransmitter Balance Disruption

The chemical structure of ALA, a five-carbon-chain ω-aminoacid, shares some similarities with those of neurotransmitters such as GABA or glutamate. Seminal studies showed that ALA acts as an agonist at presynaptic $GABA_A$ autoreceptors ($GABA_AR$), displacing GABA and tampering the depolarization-induced GABA release from preloaded nerve endings [38] [39]. Prolonged intraperitoneal treatment with ALA in rodents resulted in a decreased binding of ^{3}H-muscimol (a potent, selective $GABA_AR$ agonist) in total brain membrane preparations, a result that has been confirmed in vitro in synaptic membranes [36]. Moreover, in vitro and in vivo evidence was provided that the density of $GABA_AR$ decreases in the presence of ALA and DOVA, possibly due to selective oxidative damage (i.e., unlike broad peroxidation) [40]; in this setting, physiologic neurodevelopment could be impaired, since morphologic changes (such as a reduction in the average length of cytoplasmic processes) have been described in P19 cells [40], a cell line which represents a well-established model for studying neuronal differentiation. ALA could also have some GABA mimetic effect on pinealocytes, decreasing melatonin production [41].

It is important to acknowledge that, in clinical practice, gabapentinoids are generally viewed as safe, non-porphyrinogenic drugs for the treatment of seizures and control of neuropathic pain in AIP patients [42].

Intracerebral injections of substantial amounts of ALA are known to produce body asymmetry and convulsions in rats, preventable by glutamate receptor antagonists [43]. ALA inhibits glutamate uptake in a dose-dependent, non-competitive, and irreversible manner in rat astrocyte cultures, seemingly because of a disruption of the GLT1 subtype of the glutamate transporter (possibly related, again, to selective oxidation damage) [33]; it also non-competitively impairs glutamate uptake in synaptosomes [38].

With regard to cholinergic neurotransmission, mice receiving intraperitoneal injections of ALA showed an increase in cortex acetylcholinesterase activity after chronic treatment, whereas a reduction in cortical and an increase in hippocampal butyrylcholinesterase activity was observed after an acute treatment [5].

2.5. Other Effects of δ-Aminolevulinic Acid

Classical studies on rabbit brain microsomes and chick embryo neuronal cell cultures have shown that ALA exerts an inhibitory effect on Na^+/K^+ ATPase [44][45]. In rat cerebellar membranes, ALA impaired signal transduction by lowering the production of the intracellular second messenger cAMP, by a mechanism possibly involving direct oxidative damage to adenylate cyclase [46].

With regard to ALA and sugar metabolism, it is interesting to note that rat cerebral cortex particles displayed an increased glucose uptake (about 145%) when incubated with 2.4 mM ALA in the first hour, subsequently decreasing to around half the control values after 5 h [3]. Other studies on cerebellum particles observed a reduced glucose uptake following ALA administration (87% during 1 h incubation) [4].

3. Heme Deficiency-Induced Dysfunction

3.1. Alterations in Heme-Dependent Signal Transduction

Growing evidence is emerging in support of heme functioning as a key regulatory and signaling molecule, playing essential roles in the viability of neurons. SA-induced heme deficiency leads to impairments in nerve growth factor (NGF)-induced neuronal differentiation via the early disruption of gene expression [47][48]. In NGF-induced PC12 mature cells (rat pheochromocytoma clonal cells, resembling cells of neural crest origin and a standard model for studying neural development in vitro) SA causes caspase-dependent apoptosis, the activation of the pro-apoptotic c-Jun N-terminal kinase (JNK) and the inhibition of the pro-survival Ras-ERK 1/2 signaling pathways, with downstream inhibitory effects on the gene expression of some regulators (including p53, c-myc, PI3K, Ras, MAPK, JAK1, and MEKK1), and structural proteins (such as SVOP, NCAM, and NPY, and survival motor neuron protein), as well as the upregulation of several stress-induced genes (such as Hsp70, Hsp27, GLUT1, and transferrin receptor) [49]. Notably, mice that lack NPY expression were found to be much more susceptible to seizures [50]. The inactivation of ERK1/2 is likely linked to hypophosphorylation and the reversibly reduced expression of the N-Methyl-d-aspartate receptor (NMDAR) caused by heme depletion, with morphologic changes and neurite loss as a final result [51][52].

3.2. Cytochrome Dysfunction

In addition to oxidative damage, mitochondrial failure in AHP could also be driven by cytochrome dysfunction due to heme depletion. Of note, heme is yielded in mitochondria: following an initial series of reactions in the cytosol, coproporphyrin III is imported in mitochondria by ABCB6, a homodimeric porphyrin transporter located in the outer mitochondrial membrane, to undergo the final steps of heme biosynthesis [53]. Several alterations in brain oxidative phosphorylation have been reported in T1/T2 mice, with an increase of Complex II activity in the basal state, and a significant reduction of all four complexes after treatment with phenobarbital, compared to wild-type controls [54]. Recently, a pilot study found an altered mitochondrial bioenergetic profile in AHP patients with moderate-to-severe symptoms, who had a significantly lower oxygen consumption rate at the basal and maximal state, compared to controls and AHP patients with mild or no symptoms [55].

Somewhat unrelated to neuronal damage, it has been observed that a liver isoenzyme (CYP2A5) of the P450 cytochrome family suffers a heme-reversible inhibition in activity and mRNA levels in T1/T2 mice challenged with phenobarbital [56].

3.3. Effects on Tryptophan and Glucose Metabolism

Tryptophan 2,3-dioxygenase (TDO, formerly known as tryptophan pyrrolase) is a cytosolic hemoprotein that plays a rate-limiting role in tryptophan degradation [57]. When inhibited in the liver, plasma tryptophan build-up occurs, with augmented tryptophan brain uptake [58] and, reasonably, enhanced serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) synthesis. Early studies showed that heme-depleted rats present a dramatic reduction of hepatic TDO activity and an associated increased concentration of brain tryptophan, 5-HT, and 5-HIAA, which was almost completely reversed by parenteral administration of heme [59]. Interestingly, some authors have identified a resemblance between the neurovisceral manifestations of AHP and serotonin syndrome [59].

On the other hand, however, a combined treatment of AIA and DDC was shown to significantly impact the tryptophan metabolic pathway in rat liver in another direction: while serotonin levels decreased and tryptophan concentration rose, an unexpected dose-dependent boost of TDO activity and a reduction of saturation (holoenzyme/apoenzyme ratio) were noted, together with a dose-dependent inhibition of phosphoenolpyruvate carboxykinase (PEPCK) activity [60]. Thus, it has been speculated that the depletion of heme (and possibly pyridoxal phosphate -see below) by these porphyrinogenic drugs may lead to an enhanced substrate-mediated activity of TDO and a switch from the serotonin to the kynurenine pathway, with an increased conversion of tryptophan to kynurenine (whose formation is increased in porphyric animals [60]) and quinolinate, which is an inhibitor of PEPCK [60]. While urinary metabolome studies in AIP patients did not confirm

any differences from controls in the serotoninergic route of tryptophan metabolism, the kynurenine pathway was significantly altered with higher urinary concentrations of kynurenine and its metabolites, thus, indirectly confirming an activation of TDO [61]. Notably, PEPCK is a key enzyme in the gluconeogenetic pathway, and the occurrence of its inhibition in a porphyric setting could help to elucidate the role played by glucose in the pathogenesis of AHP. Gluconeogenesis impairment, in the form of PEPCK [62][63] or glycogen phosphorylase (GP) [62] inhibition, has been demonstrated in rats variously treated with porphyrinogenic drugs (AIA, DDC, phenobarbital, or others).

Regarding glucose utilization, ^{18}F-FDG PET scans of fasted T1/T2 mice showed a reduced glucose cerebral uptake in the primary somatosensorial and neocortex areas, which reverted to the control values after *Hmbs*-liver gene delivery. Additionally, increased levels of liver and serum ketone bodies, increased hepatic glycogen storage, and reduced pyruvate, lactate, and alanine were recorded, suggestive of a different metabolic response to fasting compared to control or *Hmbs*-liver gene supplied T1/T2 mice [64].

3.4. Effects on Nitric Oxide Synthase

From a clinical and radiological perspective, some CNS manifestations of porphyria have been likened to a picture of posterior reversible encephalopathy syndrome (PRES) [65][66]. The physiopathologic mechanism underlying PRES is generally considered to involve, together with endothelial dysfunction, a reduction of vasodilatory nitric oxide [65][67]. Nitric oxide synthases are hemoproteins, for which the prosthetic heme group is –at least in the neuronal form (nNOS)- a requisite for the dimerization of the enzyme subunits and the correct binding of substrates [68]; interestingly, they also require tetrahydro-biopteroate as a cofactor, and relative BH_4 deficiency has been linked to uncoupled reactions and the excessive production of the highly reactive species peroxinitrite [69]. NOS is also found throughout the neuronal populations of the myenteric plexus [70], where its dysfunction causes a number of dysautonomic gastrointestinal symptoms, as has been described for patients with nocturnal paroxysmal hemoglobinuria and sickle cell anemia [71][72]. Thus, an impairment in NOS activity following acute or acute-on-chronic heme depletion has been proposed as an explanation for the neurovisceral manifestation of AHP [73]. While nNOS, together with brain soluble guanylate cyclase and heme oxygenase 2, was found to maintain normal levels of activity in the brain as a whole in T1/T2 mice [56], subsequent studies in wild-type mice found a decrease of mitochondrial NOS and an increase of (inducible) iNOS glial expression following an acute ALA intraperitoneal injection [5][74]. Rats treated with SA intraperitoneal injections displayed significantly reduced nitrite/nitrate urinary output, soluble guanylate cyclase activity, kidney homogenate NOS activity, and diminished vascular sensitivity to acetylcholine and MAHMA-NONOate, a NO donor, even in the absence of overt cardiovascular dysregulation [75][76].

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