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Potential Molecular Mechanisms of 5-Aminolevulinic Acid Related to Acute Hepatic Porphyria via Transcriptome Profile Analysis

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Abstract

Acute hepatic porphyrias (AHPs) are inherited metabolic diseases that cause decreased activity or synthesis of heme biosynthesis pathway enzymes, resulting in elevated levels of 5-aminolevulinic acid (5-ALA) or porphobilinogen (PBG) in urine, stool, plasma, and organs such as the liver and brain. Our review looks at the effects of 5-aminolevulinic acid (5-ALA) on the livers of people with acute intermittent porphyria (AIP), a hereditary metabolic condition. The study discovered that 5-ALA, an α-aminoketone, can cause apoptosis, DNA damage, mitochondrial malfunction, & altered expression of carcinogen-related proteins. The researchers employed DNA microarrays to investigate the transcriptional alterations and molecular pathways in HepG2 cells after being exposed to 5-ALA for 2 and 24 hours. The findings revealed that 5-ALA '25 mM-2h' increased 10 genes related to oxidative stress response & carcinogenesis. The study also discovered that 5-ALA '25 mM-24h' enhanced pathways implicated in drug detoxification, oxidative stress, DNA damage, cell death/survival, cell cycle, and mitochondrial malfunction. The findings might help to enhance the efficacy of current medicines & lead to the creation of new biomarkers and targets for AHP/AIP diagnosis, prognosis, as well as therapy methods.

Keywords: *Acute hepatic porphyrias (AHPs), porphobilinogen (PBG), 5-aminolevulinic acid (5-ALA).*

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Introduction

Acute hepatic porphyrias (AHPs) are inherited metabolic diseases that cause decreased activity or synthesis of heme biosynthesis pathway enzymes, resulting in elevated levels of 5-aminolevulinic acid (5-ALA) as well as porphobilinogen (PBG) in urine, stool, plasma, or organs such as the liver and brain. The prevalence of AHPs is estimated to be around 5 per 100,000 people, with founder effects contributing to higher frequency. The disease has minimal penetrance, since more than 90% of heterozygotes for mutations remain asymptomatic for their whole lives. AHPs include ADP (5-ALA dehydratase deficiency), VP (variegate porphyria), HCP (hereditary coproporphyria), and AIP. (Patricia et al; 2023).

The symptoms are varied and vague, including stomach discomfort, weakness, tachycardia, black urine, and neurological problems. PBG and 5-ALA detection in urine, as well as genetic analysis, corroborate the diagnosis together with neurologic, renal, and hepatic evaluations. AHPs are often not life-threatening disorders, but therapy should be implemented to prevent various variables that might trigger or intensify episodes, including particular medicines, smoking, fasting, alcohol, hormones, & stress. (Wang et al; 2019)

Hemin and glucose infusions have been utilised to alter hepatic 5-ALA synthase 1 (5-ALAS1) expression, with hepatic or renal transplantation considered a last resort therapy. Novel therapeutics have shown that RNAi-mediated suppression of hepatic 5-ALAS1 can prevent and cure acute attacks in mice. The development of 5-ALAS1-siRNA conjugated to N-acetyl g5-ALActosamine (GalNAc), known as Givosiran, enhanced hepatic transport and enabled for the monitoring of the duration and kinetics of 5-ALAS1 inhibition without a liver biopsy. Therapies under development include adeno-associated virus 5-hPBGD gene therapy, hPBGD-mRNA delivered by lipid nanoparticles, liver-targeted rhApolipoprotein A1-PBGD, potential alternative strategies for metabolic dysfunction correction, and the enhancement of glucose therapy with insulin and insulin-sensitizers. (Longo et al; 2022)

The most frequent kind of AHP is AIP, which is caused by a 50% deficit in the hydroxymethylbilane synthase (HMBS) gene, which produces the third enzyme in the heme pathway, porphobilinogen deaminase (PBGD). AIP's chief clinical signs include intermittent acute bouts of severe stomach pain, tachycardia, nausea, neurological symptoms, and altered mental status. Furthermore, an elevated risk of hepatocellular carcinoma (HCC) in symptomatic AIP patients has been described as a long-term manifestation. (Saberi et al; 2021)

A comprehensive, matched cohort analysis of 1244 AHP patients (1063 [85%] AIP) found 108 incident HCC cases, including 83 AHP patients (6.7%) and 25 of 12,333 reference persons (0.2%). Several explanations have been postulated for the molecular mechanism underlying the development of HCC in AIP. Although the exact quantity of 5-ALA in liver cells is unknown, increased porphyrin precursors are critical in the development of symptoms. Furthermore, the level of urine 5-ALA may represent the degree of biochemical abnormalities in plasma and liver tissue. Several ideas are based on the negative effect of increased 5-ALA in the liver of AIP patients, which might foster a pro-carcinogenic milieu, raising the risk of HCC. (Lissing et al; 2022).

5-aminolevulinic acid is an α-aminoketone that oxidises to produce an enoyl radical, α-oxoaldehyde 4,5-dioxovaleric acid (DOVA), and reactive oxygen species (ROS) such H2O2, superoxide radical-anion, and hydroxyl radicals. Several in vitro and in vivo investigations have proven the harmful pro-oxidant properties of high 5-ALA concentrations. It has been shown to cause apoptosis, DNA damage, mitochondrial malfunction, & altered expression of cell cycle and apoptosis proteins in HepG2 cells. As a result, extra 5-ALA was hypothesised to operate as an endogenous pro-oxidant, contributing to the development of HCC in AIP. (Bechara et al; 2021)

Bioinformatics investigations of the DNA microarray transcriptome profiles of HepG2 cells administered 5-ALA were carried out to elucidate potential molecular pathways causing AIP pathogenesis, including HCC formation. Emerging worldwide transcriptional alterations and disrupted molecular pathways might lead to the identification of prospective biomarkers for diagnosis of AHP/AIP and prognosis for HCC, as well as promising targets for therapeutic intervention in clinical symptoms of AHP/AIP and tumour development. (Menezes et al; 2018).

Givosiran

Givosiran is a small interfering RNA (siRNA) that targets 5-aminolevulinic acid synthase, a key enzyme in the heme production pathway. Alnylam Pharmaceuticals manufactures it, and it was initially licenced for use in the United States in November 2019 to treat people with acute hepatic porphyria, a hereditary condition characterised by the overproduction of toxic heme intermediates, which causes neuro-, nephro-, and gastrotoxic effects. Givosiran is a significant step forward in the treatment of acute hepatic porphyria because it is the first approved pharmacotherapy for the prevention of acute attacks; previous strategies included non-therapeutic measures (e.g., trigger avoidance), intravenous hemin for attack treatment, and liver transplantation in refractory cases. Givosiran is the second-ever FDA-approved member of the siRNA medication class (patisiran was the first), a novel family of pharmaceuticals promising a major and exciting step ahead in the management of genetic diseases. (Bonkovsky et al; 2019).

Pharmacodynamics

Givosiran slows the production of toxic byproducts of heme synthesis in the livers of individuals with acute hepatic porphyria, avoiding their buildup and the resulting neuro-, nephro-, and gastrotoxicity. Givosiran operates at the transcriptional level, therefore it has a lengthy duration of effect and may be injected subcutaneously once a month. Although givosiran appears to be reasonably well tolerated, hepatic and renal damage were seen in clinical studies. Patients receiving givosiran should undergo regular lab monitoring of liver and renal function. (Bonkovsky et al; 2019 & Syed; 2021).

Mechanism of action

Acute hepatic porphyrias are hereditary illnesses characterised by defects in the heme production pathway in liver hepatocytes.2 The first enzyme in the route, 5-aminolevulinic acid synthase (ALAS1), is the rate-limiting step in heme production, and its activity is regulated by a negative feedback loop in the liver. Deficiencies in subsequent enzymes in the process cause low circulating amounts of heme, which encourages the up regulation of ALAS1. ALAS1 overexpression, along with downstream enzyme deficits, causes the overproduction and accumulation of toxic heme intermediates, which are ultimately liable for the neurovisceral symptoms associated with acute hepatic porphyrias. (Bonkovsky et al; 2019 & Li et al; 2021).

Givosiran is a double-stranded small interfering RNA (siRNA) that targets ALAS1 mRNA in hepatocytes. It is covalently linked to a ligand having three N-acetylgalactosamine (GalNAc) residues, which facilitates absorption into hepatocytes via asialoglycoprotein receptors (ASPGRs), which are abundantly expressed on hepatocyte cell surfaces and selective for glycoproteins containing GalNAc residues. Following endocytosis into hepatocytes, the antisense strand of givosiran is loaded into an enzyme complex known as the RNA-induced silencing complex (RISC), that utilises the antisense strand to seek out and selectively cleave the complementary mRNA sequence (in this case, between nucleotides 918 and 937 of the ALAS1 mRNA). Cleavage of the ALAS1 mRNA leads in its degradation, inhibiting the production of the ALAS1 enzyme and eventually resulting in lower circulating concentrations

of neurotoxic heme intermediates. (Bonkovsky et al; 2019 & Syed; 2021).

Absorption and Protein binding

Givosiran has steady-state Cmax and AUC24 values of 321 ng/mL and 4130 ng·h/mL, respectively, which rise proportionately with dose.5 The Tmax after subcutaneous injection is around 3 hours. The apparent centre volume of distribution is 10.4 litres.5 Both givosiran and AS(N-1)3' givosiran are predominantly distributed to the liver after subcutaneous injection. Givosiran concentration has an inverse relationship with plasma protein binding, with values ranging from 92% at 1 μg/mL to 21% at 50 μg/mL.5 It is uncertain which plasma protein givosiran binds to. (Syed; 2021)

Metabolism

Nuclease enzymes break down givosiran into shorter oligonucleotides. Its active metabolite, AS(N-1)3' givosiran, has the same potency as the parent medication, and its AUC0-24 is about 45% of the parent drug AUC at the prescribed givosiran dose.5 In vitro investigations indicate that givosiran is not a substrate of the CYP enzyme system. (Li et al; 2021).

Route of elimination and Half-life

Approximately 5-14% of the dosage recovered in urine is the unaltered parent medication, whereas 4-13% is AS(N-1)3' givosiran. Both givosiran and its active metabolite, AS(N-1)3' givosiran, have a 6-hour elimination half-life. The apparent elimination of givosiran is 35.1 L/hour. (Bonkovsky et al; 2019).

The harmful consequences of 5 ALA

5-ALA is an endogenous molecule, hence it is unlikely to be hazardous at low amounts. In non-mutated cells such as HepG2, 5-ALA is swiftly transformed to porphobilinogen, protoporphyrin IX, and heme. Previous results showed that treatment with a lower concentration of 5-ALA (2.5 mM) for 2 h and 24 h elicited up and down-regulation of genes essentially involved in mitochondrial metabolism such as MT-CO1, MT-CO2, MT-CO3, MT-ND1, MT-ND2, MT-ND3, MT-ND5, MT-ND6 (Up-regulated) and NDUFA1, NDUFB10, NDUFB3, NDUFB4, NDUFS5, NDUFS6, SDHC, UQCR10, UQCRQ (Down-regulated) or unfolded protein response such as CADVL, ARFGAP1, DNAJB11, DNAJB9, DNAJC3, EDEM1, PDIA5, SEC61A1, SRPRB (Up-regulated) (Phillips; 2019).

The harmful consequences of 5-ALA excess have long been investigated and linked to a variety of symptoms, including stomach discomfort, neuropsychiatric changes, and liver and kidney damage in illnesses characterized by 5-ALA buildup. Lead poisoning and hereditary tyrosinemia are two non-porphyria diseases with symptoms like acute hepatic porphyrias. 5-ALA (but not PBG) levels are increased. In clinical models of familial tyrosinemia, increased 5-ALA is related to the early development of HCC. (Tanguay et al; 2017).

Furthermore, due to the structural similarities between 5-ALA or the neurotransmitter gamma-aminobutyric acid (GABA), multiple investigations supported the concept that AIP patients' neuropsychiatric changes were caused by a competition between 5-ALA and GABA for GABA(A) receptors. 5-ALA and DOVA treatments on synaptosomes, neurons, and rat brains alter their shape and density while impairing GABA binding characteristics. Furthermore, 5-ALA increases rat plasma antioxidant capacity, which causes oxidative damage to brain lipids and proteins, as well as cerebral iron buildup. (Ricci et al; 2021).

In vitro, 5-ALA can be oxidised, resulting in reactive oxygen species (ROS) and the aldehyde 4,5 dioxovaleric acid (DOVA). Using comparable treatment circumstances, 5-ALA enhances ROS-induced genomic or mitochondrial DNA damage and carcinogenesis-related gene expression changes, supporting the idea that accumulating 5-ALA in the liver may predispose

individuals with AIP to develop HCC over time. (Menezes et al; 2018).

Identification of differentially expressed genes and analysis of transcriptome profiles

Although it was predicted that oxidative stress would increase the expression of antioxidant genes such as superoxide dismutase and catalase, this did not occur in the '25 mM-2h' treatment. Similarly, rat liver treated with the redox cycler Diquat does not show activation of conventional enzymatic antioxidant genes in response to oxidative stress. Instead, it shows an overexpression of p53 target genes (p21, GDF15, PLK3, ATF3, TRP53inp1, DDIT4, GADD45a, BTG2, and NDRG1), several of which play a role in the genotoxic stress checkpoint response. (Hozhabri et al; 2022).

The ATF3 gene helps to relieve stress induced by DNA damage; it plays an important function in the cell cycle by regulating the production of p21, p53, and cyclins; and it is a responsive gene to endoplasmic reticulum (ER) stress. The GDF15 gene is a member of the TGF-β growth factor superfamily associated with proliferation, survival, migration, and apoptosis. It plays critical roles in the pathogenesis of non-alcoholic fatty liver disease by regulating lipid homeostasis, protecting against hepatic steatosis by suppressing oxidative stress, mitochondrial damage, dsDNA release, and activating AIM2 inflammasomes. Furthermore, GDF15 gene expression is favourably correlated to protoporphyrin in erythropoietic protoporphyria. HMOX1 protein cleaves heme to produce biliverdin, carbon monoxide, and ferrous iron during heme catabolism. Aside from its critical significance, HMOX1 participates in the cellular response to oxidative stress, cancer cell proliferation, and chemoresistance. AKR1B10 is a gene important for aldehyde metabolism, and its overexpression under 5-ALA therapy may be connected to the existence of DOVA, the last aldehyde of 5-ALA oxidation. (Luu et al; 2021).

Furthermore, AKR1B10 has emerged as a possible biomarker for HCC diagnosis and prognosis; it influences HCC development and progression, as well as acquired resistance to various chemotherapeutic treatments. One of the prevalent DEGs in our research, c-JUN, codes for a protein kinase of the MAPK family that plays a crucial role in a wide variety of cellular responses, such as proliferation, differentiation, their survival, migration, invasion, & apoptosis, leading to the development of HCC. (Wang and Tai; 2016).

The MAP3K8, MBNL2, & GADD24A genes are specific to 5-ALA '25 mM-2h'. Overexpression of MAP3K8 is a strong predictor of poor survival rates in many cancer patients. The MBNL2 gene encodes a splicing regulatory protein that functions as a tumor suppressor in hepatocarcinogenesis. GADD45A is a growth arrest & DNA damage-inducible gene that may be related with DNA damage caused by 5-ALA's pro-oxidant characteristics, as found in earlier studies using the same exposure period and 5-ALA concentration. It is also worth noting the up regulation of two long non-coding RNAs (lncRNAs): the functional pseudogene NMRAL2P and LINC01909, the function of which is unknown. Some lncRNAs have already been implicated in many biological processes, including tumour development and metastasis in hepatocellular carcinoma. NMRAL2P is a downstream regulator of Nrf2 signalling pathways implicated in oxidative stress, cancer, neurodegeneration, & diabetes, as well as cardiovascular, renal, & liver illnesses. (Chen et al; 2018).

A comparison of our gene profile to the gene expression signature of HepG2 cells employing the Library of Integrated Network-Based Cellular Signatures (LINCS) identified the substances and their modes of action, which showed elevated gene profiles comparable to 5-ALA (Table S7). Most of the chemicals are categorized into four primary categories of mechanisms of action. 1) EGFR inhibitor (canertinib, neratinib, afatinib), 2) HDAC inhibitor (mocetinostat, entinostat, belinostat), 3) MEK inhibitor (PD-184352, PD-0325901, selumetinib), and 4) mTOR inhibitor (OSI-027, sirolimus, AZD-8055, etc). Analyzing each

target of the chemicals, we discovered that they are all engaged in signaling pathways controlled by oxidative stress. (Arfin et al; 2021).

Pathways and functional enrichment analyses

The 5-ALA '25 mM-24h' showed enriched pathways in all four databases. KEGG and GO (Fig. 4, Fig. 6) revealed up-regulated genes that enriched pathways linked to xenobiotic detoxification via the reduction of ketone and aldehyde carbonyl functional groups by the aldo-keto reductase (AKR) family. These processes might be linked to the detoxification of 5-ALA excess and its ultimate oxidation product, the aldehyde DOVA. Furthermore, AKR1B10 is a unique marker of hepatocellular carcinogenesis through regulation of proliferation, apoptosis, or chemoresistance. (DiStefano and Davis; 2019).

Several oxidative stress pathways were enriched, supporting the widely recognized theory that 5-ALA induces an oxidative environment, which causes cellular damage such as lipoperoxidation, DNA base oxidation, and mitochondrial malfunction. Furthermore, melatonin lowers the oxidative environment and decreases 5-ALA while PBG levels in a rat model of drug-induced porphyria, and levels of antioxidant enzymes rise in the blood of AIP patients. (Wang et al; 2019).

Numerous genes of the respiratory electron transport chain or hepatic mitochondria biogenesis have been increased in phenobarbital-induced AIP mice, suggesting mitochondria may play an important role in the aetiology of AIP symptoms. Our findings corroborate investigations on the viability of using mitochondria oxygen consumption rate in blood for a possible biomarker of biochemical or clinical aspects of certain kinds of porphyria. (Chen et al; 2019).

Furthermore, oxidative stress may be linked to pathways associated with senescence, cell cycle control, cell death, proliferation, or the endoplasmic reticulum's stress response. The creation of ROS and the activation of inflammatory processes are inextricably linked, with low-grade chronic inflammation a hallmark of metabolic diseases and carcinogenesis. Patients with AIP have elevated systemic levels of cytokines, chemokines, and growth factors. Furthermore, 5-ALA, PBG, and numerous other porphyrins can behave as damage-associated molecular patterns (DAMPs) that may be connected to TLR receptor pathways. (Storjord et al; 2017).

First-Neighbors Network for 5-ALA ‘25 mM-24h’

MAPKs respond to cytokines by activating inflammatory genes that are involved in cell death and survival pathways. A variety of pathways linked to dysregulated JAK-STAT functioning can cause immune deficiency disorders and malignancies. One of the effectors of the JAK/STAT pathway in our network was the proto-oncogene PIM-1, which is involved in cell survival and proliferation and provides a selective advantage in carcinogenesis. (Tao et al; 2013).

The Wnt/β-catenin pathway protects hepatocytes from oxidative stress and interacts with Rho GTPases, which may contribute to hepatocarcinogenesis. essentially β-catenin was not a DEG, knockout mice for the Wnt/β-catenin pathway submitted to a diet that included the porphyrinogenic agent 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC), offer a lower rate of protein aggregation, modified proteasome activity, and diminished autophagic processes, thereby lowering liver damage triggered by the accumulation of porphyrins and their precursors. The complex AP-1 (FOS-JUN) regulates cell proliferation, differentiation, and transformation. C/EBPbeta controls the acute phase response and inflammation, and it may potentially play a role in liver regeneration. EGR1 responds to growth factors, DNA damage, hypoxia, cell survival, proliferation, or death. (Saggi et al; 2019).

Furthermore, 5-ALA upregulates the SQSTM1 gene, which codes for sequestosome/p62, a

protein involved in the crosstalk between the ubiquitin-proteasome system (UPS) and autophagy, and this can degrade aggregated proteins such as Mallory-Denk bodies found in alcoholic and non-alcoholic hepatitis, as well as the liver of rats fed the porphyrinogenic agent DDC. The oxidative stress generated by fluorescent porphyrins of cutaneous & photosensitive porphyrias may result in protein aggregation, leading to proteostasis dysfunction and tissue injury. (Lahiri et al; 2016).

The improper regulation of the proteostasis network can't be ignored in AIP, and it is one of the possible target techniques recommended for treatment. The potential effectors cyclin D1 & GADD45B can cause cell cycle arrest and checkpoint activation in reaction to DNA damage. The genotoxicity of 5-ALA as its derivatives is widely characterized in the literature, both in vivo and in vitro. (Murray and Carr; 2018).

Exogenous 5-ALA is addressed to the heme mitochondrial biosynthesis pathway, which suppresses 5-ALAS1 by negative feedback. Accumulation of 5-ALA and heme can boost the expression of HMOX1, which has been linked to immunoregulatory responses and carcinogenesis. 5-ALA's mechanism of action has recently been linked to immune system mobilisation. PBGD Hmbs−/− knockout mice injected weekly with hemin exhibit porphyrin-induced inflammation, increased cytokine expression in the liver, or activation of macrophages. (Schmitt et al; 2018).

Overall, 5-ALA '25 mM-24h' increased biological processes such as drug detoxification, oxidative stress, DNA damage, promotion of cell death/survival, cell cycle change, and mitochondria malfunction, confirming 5-ALA's pro-oxidant capabilities. Although additional confirmation is necessary, our data revealed the participation of several probable biological processes in 5-ALA toxicity, such as senescence, immunological responses, endoplasmic reticulum stress, and certain putative effectors, such as sequestosome/p62, osteopontin, or lon peptidase 1. (Gibellini et al; 2020).

Conclusions

Our review added to our understanding of the molecular mechanisms of 5-ALA toxicity, highlighting that 5-ALA excess might cause damage to biomolecules as well as disrupt molecular pathways that regulate oxidative reactions. Additional investigations including the loss of function of potential genes will be conducted to confirm the molecular pathways or cellular processes addressed by 5-ALA, as well as to explain its involvement in the pathophysiology of AHP/AIP or HCC formation.

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