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Regulating mitochondrial metabolism by targeting pyruvate dehydrogenase with dichloroacetate, a metabolic messenger

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Abstract

Dichloroacetate (DCA) is a naturally occurring xenobiotic that has been used as an investigational drug for over 50 years. Originally found to lower blood glucose levels and alter fat metabolism in diabetic rats, this small molecule was found to serve primarily as a pyruvate dehydrogenase kinase inhibitor. Pyruvate dehydrogenase kinase inhibits pyruvate dehydrogenase complex, the catalyst for oxidative decarboxylation of pyruvate to produce acetyl coenzyme A. Several congenital and acquired disease states share a similar pathobiology with respect to glucose homeostasis under distress that leads to a preferential shift from the more efficient oxidative phosphorylation to glycolysis. By reversing this process, DCA can increase available energy and reduce lactic acidosis. The purpose of this review is to examine the literature surrounding this metabolic messenger as it presents exciting opportunities for future investigation and clinical application in therapy including cancer, metabolic disorders, cerebral ischemia, trauma, and sepsis.

Keywords

Dichloroacetate; Mitochondria; Lactic acidosis; Glycolysis; Energetics

1. Introduction

Dichloroacetate (DCA) is a naturally occurring investigational drug that first demonstrated potential for clinical use over 50 years ago by lowering blood glucose, first in animals, and subsequently in humans [1,2]. It is a small, halogenated carboxylic acid with a very limited number of important sites of action that have demonstrated increasingly diverse clinical applications [3]. Its ability to modulate a key process in cellular respiration has made it an

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Nick Schoenmann: Conceptualization, Writing, Editing; **Nicholas Tannenbaum:** Writing, Editing; **Ryan M. Hodgeman:** Writing, Editing; **Raghavan Pillai Raju:** Conceptualization, Writing, Supervision.

Declaration of competing interest

Authors have no interest to declare.

intriguing target that continues to be investigated for application in the treatment of tumors, metabolic diseases, cerebral ischemia, and trauma.

2. Pyruvate dehydrogenase complex: the gatekeeper of mitochondria

The primary mechanism of interest for DCA has been centered around its direct modulation of the mitochondrial pyruvate dehydrogenase complex (PDC)/pyruvate dehydrogenase kinase (PDK) axis (Fig. 1). It has also been shown to act as an inhibitor of HMG-CoA-reductase and an irreversible inactivator of glutathione S-transferase zeta 1 (GSTZ1) [4–6].

PDC is a mitochondrial multienzyme complex that plays the paramount role as a gatekeeper in connecting cytoplasmic glycolysis with the tricarboxylic acid cycle and eventual oxidative phosphorylation. The rate-limiting step in this process involves oxidative decarboxylation of pyruvate leading to the production of acetyl-CoA, NADH, and CO_2 [7,8]. PDC is a tightly regulated composite of three different catalytic enzymes: pyruvate dehydrogenase (E1), dihydrolipoamide acetyltransferase (E2), and dihydrolipoamide dehydrogenase (E3). These constituents act in concert as a primary regulator in mitochondria linking glucose metabolism, fatty acid metabolism, and the Krebs' cycle.

Regulation of PDC is achieved through a cycle of phosphorylation and dephosphorylation which takes place at three serine residues, Ser293, Ser300, and Ser232, of the alpha-subunit of pyruvate dehydrogenase (PDH) [9]. The reversible phosphorylation of PDH by PDK leads to inactivation, and dephosphorylation by pyruvate dehydrogenase phosphatase (PDP) reactivates the complex [8,10,11]. PDK is activated by increased levels of acetyl-CoA and NADH and inactivated by the presence of pyruvate. Importantly, PDK activity is also increased by hypoxia.

Four isoforms of PDK have been identified in humans: PDK1, PDK2, PDK3, and PDK4. Under normal physiological conditions, the four isoenzymes are predictable in both distribution and expression: PDK1 is predominantly expressed in the heart, pancreatic islets, and skeletal muscles. PDK2 is broadly distributed in many tissues, except for the lung and spleen. PDK3 is found in the testicle, kidney, and brain. PDK4 is distributed in the heart, skeletal muscle, liver, kidney, and pancreatic islets [12]. However, both distribution and expression are altered under various pathologic states. Abnormal regulation of PDK2 and PDK4 has been associated with diabetes mellitus, whereas all four isoenzymes have been found to have a varied expression in different malignant tumors [12].

3. Dichloroacetate metabolism

In vivo, DCA is primarily metabolized via biotransformation executed by the zeta-1 family isoform of glutathione transferase (GSTZ1), also known as maleylacetoacetate isomerase (MAAI) (Fig. 2) [13]. This enzyme primarily resides in hepatocytes and proximal tubule cells of the kidney where it also serves to perform the final steps of tyrosine and phenylalanine metabolism [14]. Initially, DCA is transformed into glyoxylate, a highly reactive molecule that can cause oxidative stress to tissues and requires further metabolization [15].

Glyoxylate is readily oxidized to oxalate via lactate dehydrogenase [16,17]. The oxalate is further metabolized via glyoxylate carboligase in a thiamine-dependent reaction to α-hydroxy-β-ketoadipate, a highly soluble molecule that is renally eliminated [18]. It was posited that the reversible polyneuropathy seen with DCA may be due to thiamine deficiency as thiamine stores are depleted through this reaction [19]. Case studies have also reported peripheral neuropathy from oxalate deposition in peripheral nerves and other tissues in primary hyperoxalurias, highlighting the metabolism to oxalate as a clinically significant event [20–22]. Through an alternative pathway, glyoxylate is also metabolized in peroxisomes and mitochondria (Fig. 2). Hepatocytes are rich in alanine glyoxylate aminotransferase which allows for abundant peroxisomal transformation to glycolate and subsequent breakdown to glycine which is used in several intracellular pathways [16].

DCA appears to restrict its own metabolism via inhibition of GSTZ1/MAAI and thus as DCA concentrations rise in the body via repeated administration or higher dose usage, the plasma clearance of the drug decreases [23,24]. Clearance of DCA from the plasma has been shown to be age-dependent, with older patients demonstrating decreased DCA clearance [25]. Both animal and human evidence have highlighted the importance of GSTZ1 genetic polymorphisms and their consequent influence on the metabolism of DCA, suggesting that individualized dosing regimens may be required to adequately address issues related to treatment effectiveness and adverse effects [24,26,27].

4. Lactic acidosis

Lactic acidosis is manifested when the production of lactic acid exceeds its clearance. Congenital lactic acidosis is generally a result of mitochondrial dysfunction due to deleterious mutations in genes coding for key proteins involved in mitochondrial function. As a result, cells are forced to rely on glycolysis as a primary means of energy production and suffer subsequent organ damage. Most cases prove fatal in the long term. DCA was proposed as a possible solution through enabling oxidative phosphorylation and consequent lowering of lactate.

Stacpoole and colleagues showed that DCA lowers blood, cerebrospinal fluid, and intracellular lactate in a dose dependent but not time dependent manner [28]. Barshop et al. performed a small open-label study in which 37 patients with “various mitochondrial disorders” were treated with DCA for a mean of 3.25 years though the treatment course ranged 3 weeks to 7 years. A subjective impression of overall disease showed improvement in nearly half of the patients (48.6 %) though the variability of underlying genetic disease, the open-label nature, and the discrepancies in treatment length made these findings difficult to generalize [29]. In a previous study using DCA as a potential therapeutic for all comers with lactic acidosis, there was a statistically significant decrease in the lactate level in arterial blood, but this did not translate to improved hemodynamic parameters or overall survival in a larger cohort of patients [30]. In another study, DCA was tested in congenital lactic acidosis. It was well tolerated orally and blunted post-prandial lactate but did not improve neurologic function or any other measured clinical outcome. [31] Thus, despite its success in lowering lactate, there does not as of yet appear to be a benefit in mortality from

DCA use in congenital lactic acidosis [30]. This is likely due to the devastating nature of the pathophysiology and the site of mitochondrial gene mutations [32].

5. Diabetes mellitus

DCA has been studied in various metabolic diseases, including diabetes mellitus (DM). In animal models, DCA lowered the serum blood glucose of diabetic mice though no change was observed in healthy mice [1]. It was observed that DCA reduces the plasma glucose concentration in starved and diabetic rats, but not in normal, fed rats [4,33]. Later, Stacpoole and Greene found that DCA decreased hepatic gluconeogenesis and average glucose levels without an increase in insulin secretion in diabetic BB Wistar rats. The authors concluded that this decrease in glucose is likely due to reduced production of lactic acid and alanine, and subsequent disruption of the Cori cycle for gluconeogenesis [34]. A recent study in ob/ob mice also attributed the effect of DCA on blood glucose to the suppression of hepatic gluconeogenesis [35]. DCA improved diabetic outcomes in mice treated with streptozotocin (STZ), a selective toxin for pancreatic beta cells. Furthermore, di-isopropylammonium dichloroacetate (DIPA), a derivative of DCA, was also shown to improve survival in STZ-diabetic rats [36].

DCA exhibits cardioprotective effects in the setting of diabetic cardiomyopathy and it has been shown to increase peripheral glucose oxidation which may ameliorate microvascular ischemic changes within cardiac muscle [37]. Additionally, DCA improved cardiac contractility in decompensated congestive heart failure, increased cardiac function and overall survival, as well as decreased oxidative stress and prevented cell death in cultured cardiomyocytes [38]. In ischemic cardiac cells, DCA was able to reduce ischemia/reperfusion damage via an AMPK-mediated mechanisms [39,40]. There is a paucity of studies that tested DCA’s ability to counteract heart failure or improve cardiac contractility in diabetic mice. Outside of cardiac damage, diabetes has been associated with improper endometrial function and ovarian damage. The administration of DCA improved endocrine and reproductive function in rat models [41]. Despite all this, concerns about the long-term safety of DCA continue to limit its use as a chronic diabetic therapy [3].

6. Cancer

DCA has also been studied more recently in the treatment of cancer. The oxygen and energy demands of rapidly growing malignant cells are generally not met by the preexisting vascular supply [42]. The reduced intracellular oxygen leads to the stabilization of HIF-1α which regulates the release of vascular endothelial growth factor alpha (VEGF-A) [43]. Cancer cells generate new blood vessels in response to hypoxia through a VEGF-A-dependent process termed pathological angiogenesis [44]. VEGF-A also promotes lymphogenesis which potentiates lymphatic metastasis of cancer [45]. DCA has been shown to limit HIF-1α production by tumor cells, upregulate P53 and subsequent apoptosis, and reduce VEGF-A activity in brain glioblastoma multiforme [46].

A hallmark of cancer cells is the use of the anaerobic glycolytic pathway despite the presence of oxygen and glucose [47]. This aerobic glycolysis was later termed “The

Warburg Effect.” Liberti et al. posited that the Warburg effect conferred a benefit to cancer cells through the rapid availability of energy provided by glycolysis, the shunting of anaerobic byproducts to other biosynthetic pathways, aiding in immune cell evasion, and cell signaling through reactive oxygen species (ROS) [48]. Aerobic glycolysis is preferentially used by tumor cells through TGF-β1 signaling, a process also observed in endometriosis [49]. It was suggested that DCA inhibits cancer progression through a reversal of the Warburg effect [50]. By forcing pyruvate through oxidative phosphorylation, the mitochondrial suppression exhibited by cancer cells is reversed; ultimately promoting apoptosis [50]. Cancer cells also use VEGF and other HIF-1-mediated actors to increase angiogenesis in an acidotic environment. [43] This enables cancer cells to gain access to blood vessels and promote metastasis. DCA is able to mitigate this by reducing lactic acidosis in the tumor microenvironment [51]. Finally, fatty acid oxidation is required for new nucleotides to be formed in order for cancer cells to replicate [52]. DCA can suppress mitochondrial betaoxidation, at least in mammalian muscle and liver, making it more difficult for cancer cells to generate the nucleotides necessary to replicate and stimulate endothelial growth [51,52].

DCA is also able to boost host cell immunity through indirect means. An elevated serum lactate can blunt T-cell proliferation and signaling via cytokines [53]. It was also observed to decrease glutathione levels in T-cells, making them more sensitive to ROS and subsequent T-cell apoptosis. It was found that in vitro treatment of cancer cells in the setting of DCA improved T-cell function, signaling, and survival which led to decreased cancer growth [53]. Thus, DCA appears to reinforce the host immune system to better identify and respond to tumor cells.

Research in the last decade has shown that DCA increases certain cancer cells’ sensitivity to radiotherapies and chemotherapies while decreasing the side effects of common chemotherapy agents. In colorectal cancer cells that were previously resistant to 5-fluorouracil (5-FU) treatment, the in vitro addition of DCA lead to increased chemosensitivity to 5-fluorouracil while increasing the intracellular level of intrinsic tumor suppressor p53. This vastly reduced tumorigenesis [54]. DCA has been used in trials with several other agents, such as cisplatin and arsenic trioxide, showing improved apoptosis, anti-proliferative effects, and increased treatment effectiveness in both lung and breast cancer, as well as playing a nephroprotective role in the treatment of breast cancer. [55–57]. Galgamuwa et al. were able to show that DCA played a nephroprotective role in the management of breast cancer with cisplatin without limiting the overall effectiveness of treatment [58]. It has also been linked to increased radiosensitization of tumors in breast cancer and gliomas [59,60]. One case report showed remission in a man with relapsed non-Hodgkin’s lymphoma after DCA treatment [61]. Furthermore, when DCA was added to chemoradiotherapy for locally advanced head and neck squamous cell carcinoma, though survival rates were not significantly different between groups, the DCA group had significantly reduced pyruvate and lactate [62].

One of the notable limitations of chronic DCA use (discussed further below) has been the peripheral neuropathy [5,13,26,63]. This adverse effect may be mitigated using antioxidant medications or even muscarinic antagonists and proves to be reversible as well [5]. Despite

this side effect, recent data show DCA may mitigate the toxic effects of other chemotherapy agents. A common side effect of the chemotherapeutic agent bleomycin is pulmonary fibrosis mediated by lung myofibroblasts. This is posited to occur due to HIF-1α induction in the lungs leading to myofibroblast proliferation. DCA can downregulate the HIF-1α response leading to attenuation of myofibroblast proliferation and subsequent decrease in pulmonary fibrosis [64]. Doxorubicin, when co-administered with DCA, was found to be more tumor-selective than doxorubicin alone with similar chemotherapeutic potential [65]. Furthermore, it was found that DCA successfully decreases doxorubicin's characteristic cardiotoxicity [66]. The pre-clinical and clinical studies show that the induction of glycolytic-mitochondrial shift and its anticancer effects have the potential to alter cancer metabolism and cancer progression and offer promise for further studies.

7. Ischemia and reperfusion

7.1. Trauma

For decades trauma has been cited as the leading cause of death in people under the age of 45, with hemorrhagic shock noted as the most common preventable cause of death in this subgroup [67–69]. Hemorrhagic shock leads to global tissue hypoxia, decreased coronary perfusion pressure, and subsequent depressed cardiac function, all of which led to an inevitable downward spiral of worsening hypoperfusion and dysfunction [70]. The treatment of hemorrhagic shock has evolved from large volume replacement with crystalloid in order to maintain a degree of tissue reperfusion and continued metabolic activity to a more straightforward "replace blood with blood" strategy, although this approach is limited by the logistical challenges of acquisition and storage [71]. This is particularly true for the far-forward management of patients in combat zones and rural emergency departments. Although more advanced tourniquets, kaolin-impregnated gauze ("combat gauze"), and other adjuncts have become standard measures, the number of trauma-related victims remains high, and other means of significantly improving survival are lacking.

Several studies have demonstrated diminished mitochondrial function in hemorrhagic shock [72–74]. On a metabolic level, hemorrhagic shock leads to hypoxia, and this scarcity of cellular oxygen suppresses mitochondrial oxidation through increased activity of glycolytic enzymes and PDK [75,76]. The subsequent inactivation of PDC by PDK may be a mechanism to reduce excess production of ROS, but at the cost of the more economic production of ATP [77]. Investigations using animal models have demonstrated the profound effect of DCA to enhance mitochondrial function within the context of hemorrhagic shock injury (HI) both as monotherapy and as part of a combinatorial strategy [74,78]. Rats subjected to HI using validated hemorrhagic shock models exhibited prolonged survival independent of the addition of volume resuscitation when treated with DCA. The elevated levels of PDK in rats subjected to HI that received DCA were restored to normal. DCA was shown to be superior to another mitochondria potentiating agent, resveratrol, by almost doubling the mean survival time of subjects (200 vs 110 min) [78,79]. Some of the earlier studies using higher doses of DCA in HI had mixed results [80,81]. It is worth noting that the method of inducing HI and the relatively high doses of DCA (150 mg/kg vs 10–25 mg/kg) used in the previous studies may have acted as confounding factors [80,81].

Although future studies will need to investigate both the efficacy and the safety of the drug in human patients, the single-dose regimen could be valuable in austere situations and avoids the well-known peripheral neuropathy observed with chronic use [5,39].

7.2. Sepsis and inflammation

Initial lactate build-up as a response to an acute disease state contributes to a heightened inflammatory and immune response. When the body's regulatory mechanisms are overwhelmed, this initially favorable response can lead to shock, increased morbidity, and death [82–84]. Lactic acidosis is a key marker of sepsis and septic shock with elevated levels associated with worse outcomes [84,85]. Lactic acidosis in sepsis primarily originates from the byproducts of anaerobic respiration due to tissue hypoxia and the mitochondrial-glycolytic shift during periods of shock due to reduced microcirculation [84] The effect of DCA on the PDC limiting the transition to anaerobic respiration makes it an interesting adjunct therapy in the setting of sepsis and septic shock.

In 1992 a clinical trial in patients with lactic acidosis showed no improvement of morbidity or mortality in a randomized controlled study of 252 patients using DCA vs. placebo. In the study over half (~58 %) of the patients had sepsis as the cause of their lactic acidosis, however sub-group analysis was not reported [30]. Studies have shown clearance of lactic acidosis does not correlate directly to improved outcomes in sepsis, making the results difficult to interpret given trial participants had proven lactic acidosis >5.0 mmol/L prior to initiation of DCA therapy [30,82,84]. Notably, this trial was completed prior to the Surviving Sepsis Campaign in 2002 and treatment for the disease state has shifted dramatically.

Research continued in this sphere, using in vivo and in vitro models, to show how DCA's effect on PDK lead to increased survival in septic mice [86]. They postulated that cellular divergence to less efficient energy production during times of oxidative stress can contribute to increased mortality by creating an environment favorable to endotoxins while limiting the function of the immune system [86].

In 2020, Bakalov et al. used Drosophila models to show that DCA in combination with antibiotics lead to longer overall survival in septic flies with no effect on sham control groups [82]. This study further reported that septic flies who received DCA had significantly lower levels of lactic acid, α-ketoglutarate, and pyruvate levels. These levels were unchanged in flies without infection regardless of DCA therapy leading us to conclude that the effect of DCA was disease-state specific [82].

Numerous studies have suggested that organisms with sepsis not only undergo cellular hypoperfusion but experience a cascade of metabolic shifts favoring anerobic respiration causing negative downstream effects. In these studies, manipulation of PDC has shown a reversal of these rearrangements by reliance on aerobic respiration through the TCA cycle [84,86–90]. Mainali et al. showed this metabolic shift specifically led to the inactivation of mitochondrial respiration through PDK1 inhibition of PDC causing significant prolonged liver injury limiting our internal sepsis recovery mechanisms [88]. Their findings also suggest a role for stress hormone pathway in sepsis-induced PDK activation. DCA has

shown improved homeostasis, energy balance, and reduction of the inflammatory cascade with modulation of PDC in animal models, however no randomized controlled clinical trial in the setting of sepsis has been done.

7.3. Cerebral ischemia

DCA has been shown to have a significant role in pre-clinical studies as a potentially neuro-protective agent during cerebral ischemic and reperfusion events by modulating PDC activity [91–96]. Local tissue hypoxemia as the result of vessel occlusion leads to cell death, dysfunction, inflammation, and eventual breakdown of the blood-brain barrier (BBB) [91,92,94,97]. Like other pathologic states, inhibition of PDC leads to decreased oxidative phosphorylation [92,93]. In 1994 Dimlich used DCA in gerbil models to show evidence of reduced neurological damage after ischemia [95]. High dose DCA was used in a clinical trial for patients presenting 1–5 days after acute stroke. After a single high dose there was a lactate to *N*-acetyl compound ratio trend suggesting possible therapeutic benefit [98].

Further research has shown that the accumulation of NADPH and ROS species during the initial cerebral ischemic insult can cause worsening neuronal tissue damage after reperfusion. ROS disrupts the BBB leading to pro-inflammatory infiltration and edema. [94,97,99] The ability of DCA to mitigate the production of ROS in addition to increased energy availability at the site of injury provides a multifactorial advantage in the setting of cerebral ischemic pathology. Hong et al. showed in 2018 that an infusion of DCA and pyruvate in rat models reduced neuronal cell death and limited the downstream effects of neuroinflammatory response. However, they did not show improvement with DCA alone [97]. Zhao et al. in 2021 showed that DCA administration during cerebral ischemia and reperfusion was able to reduce infarct size, cerebral edema, and improve the integrity of the BBB in a murine model [94].

Data suggests that DCA may have a role in mitigating cerebral ischemic changes and negative downstream effects in the setting of cerebrovascular accident, however, animal models were dosed at the time of injury bringing into question the clinical applications of the data [94,95,97] Clinical trials using DCA in the setting of cerebral ischemia are warranted to take this orphan drug from bench to bedside.

8. Limitations of use

Dichloroacetate has been studied in clinical trials for several decades and used with limited FDA approval as an orphan drug for metabolic disorders. These trials have established a robust safety profile. DCA has been associated with neuropathic toxicity and sub-clinical hepatic enzyme elevation, with neuropathy the most frequently reported significant finding [13,26,29,31,63,100–106]. Adverse events trend towards transient, even with reported cases of mild to severe peripheral neuropathy [26,29,101,105]. In a trial presented by Kaufmann et al., peripheral neuropathy was the cause of prematurely stopping therapy for 19 of 22 patients treated with high doses of DCA (25 mg/kg/day) for a rare but progressive mitochondrial disease affecting the neurologic system termed mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). However, symptoms resolved completely in 17 of the 19 patients with the remaining two patients lost to follow-up [63]. Other

trials with chronic DCA use in similar settings did not show similar neuropathic toxicity [29,31,101–104,106]. The three trials that used limited dosing did not report neuropathy or any other clinically significant side effects [30,98,107].

A deeper look into the dosing of DCA investigated biomechanical modifiers and genetic predispositions to drug DCA metabolism suggesting that sex, age, and a testable gene (GSTZ1) have a significant influence and should be considered when dosing [26,63,100]. Published studies have not shown severe life-threatening or chronically disabling toxicity associated with the use of DCA in pre-clinical or clinical studies. DCA continues to be investigated in both acute and chronic settings with variable dosing structures. The possibility of short-term therapy, particularly in severe acute illness, should not be limited by its published side-effect profile.

9. Conclusion

DCA represents a potentially limitless opportunity for investigation. The PDC/PDK axis can be modulated by DCA in such a way to negate the body's adaptive preference for glycolysis under pathologic states and instead dramatically increase the efficiency of energy production through aerobic respiration. Despite over fifty years of use as an investigational drug with numerous potential clinical applications, there are still a dearth of clinical trials focused on the efficacy of this metabolic modifier in humans. Although many inquiries surrounding the use of DCA have centered on its ability to reverse the Warburg effect in the setting of malignancy, recent work has also shown promise in the acute setting of cerebral ischemia-reperfusion injuries, hemorrhagic shock, and sepsis. These areas of clinical interest are particularly exciting given that the most often cited and well-studied adverse effect of DCA is its potential to cause reversible peripheral neuropathy in the setting of chronic administration [5]. These acute disease processes are generally short in duration; therefore, drug administration requirements would likely be limited to a single dose or brief regimen [74,78,90]. Future studies should seek to prove the efficacy of DCA in the aforementioned clinical contexts and validate its safety suggested by studies already reviewed. It is possible that this orphan drug and its successors will find several homes within the house of medicine.

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Data availability

No data was used for the research described in the article.

Abbreviations:

DCA	Dichloroacetate
PDK	Pyruvate dehydrogenase kinase

PDH	Pyruvate dehydrogenase
PDC	Pyruvate dehydrogenase complex

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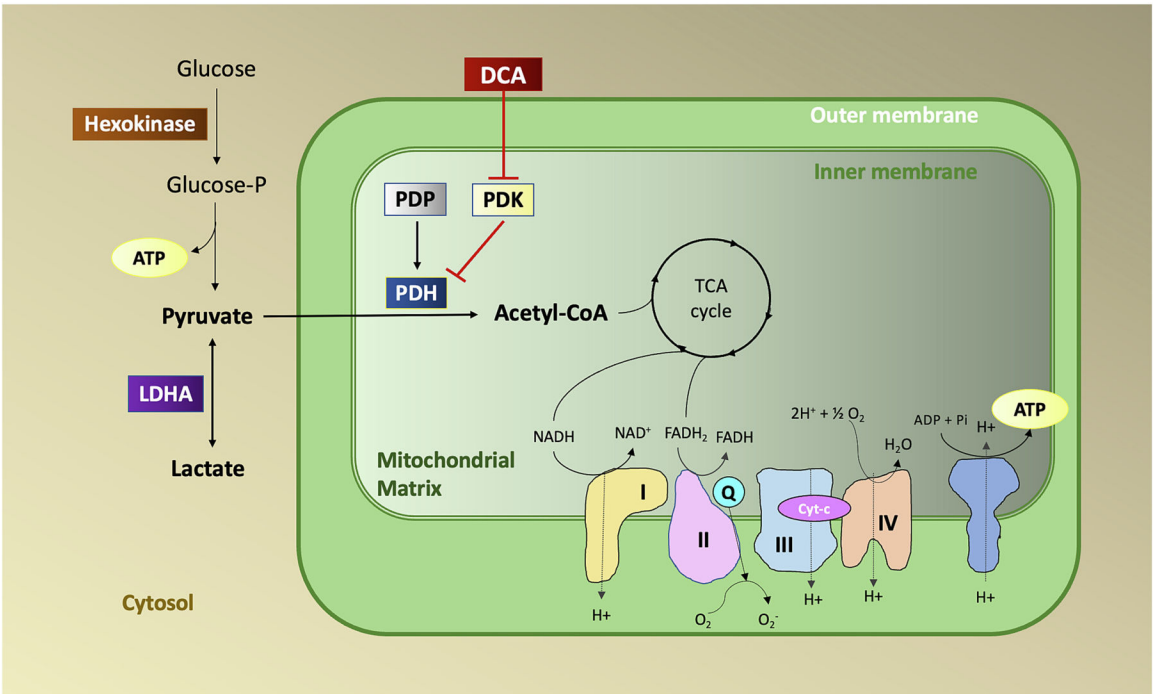

Fig. 1.

Mechanism of action of dichloroacetate (DCA). PDK phosphorylates and inhibits the activity of PDH while PDP dephosphorylates and activates PDH. Under hypoxic conditions activation of PDK results in phosphorylation and inactivation of PDH and reduced conversion of pyruvate to acetyl CoA. DCA inactivates PDK resulting in the activation of PDH.

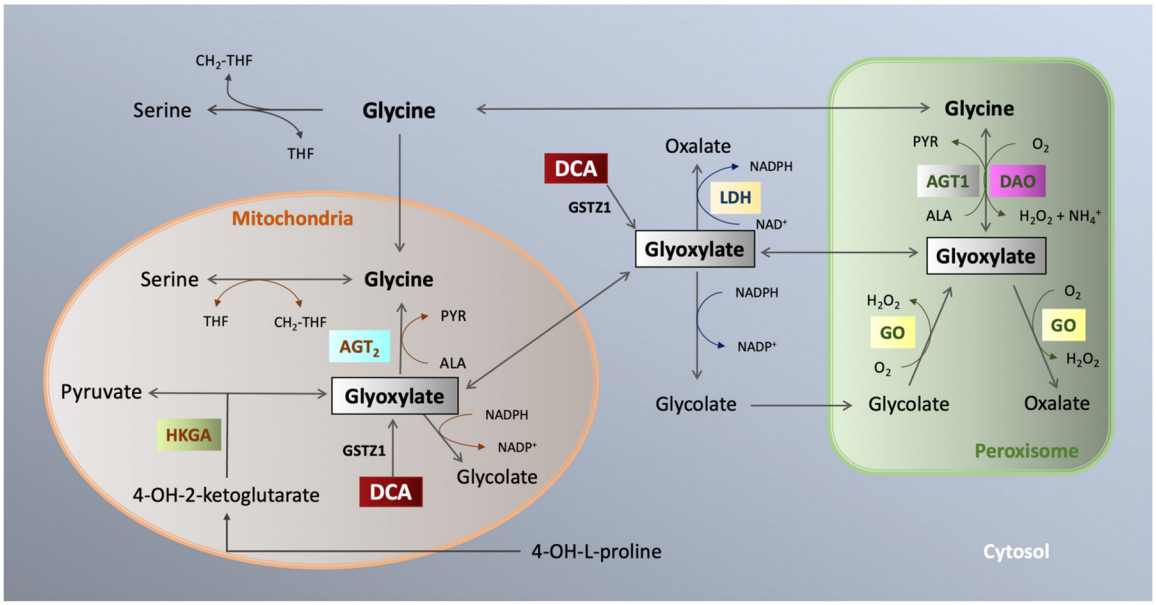

Fig. 2.

Dichloroacetate metabolism. GSTZ1 metabolizes DCA to glyoxylate which metabolizes to glycine, pyruvate, or oxalate in the mitochondria or peroxisome.