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Therapeutic applications of dichloroacetate and the role of glutathione transferase zeta-1

Margaret O. James [a,*], Stephan C. Jahn [a], Guo Zhong [a], Marci G. Smeltz [a], Zhiwei Hu [a], Peter W. Stacpoole [b,c]

[a] Department of Medicinal Chemistry, University of Florida, Gainesville, FL 32610-0485, United States
[b] Department of Medicine, University of Florida, Gainesville, FL 32610-0226, United States
[c] Department of Biochemistry and Molecular Biology, University of Florida, Gainesville, FL 32610, United States

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ABSTRACT

Dichloroacetate (DCA) has several therapeutic applications based on its pharmacological property of inhibiting pyruvate dehydrogenase kinase. DCA has been used to treat inherited mitochondrial disorders that result in lactic acidosis, as well as pulmonary hypertension and several different solid tumors, the latter through its ability to reverse the Warburg effect in cancer cells and restore aerobic glycolysis. The main clinically limiting toxicity is reversible peripheral neuropathy. Although administration of high doses to rodents can result in liver cancer, there is no evidence that DCA is a human carcinogen. In all studied species, including humans, DCA has the interesting property of inhibiting its own metabolism upon repeat dosing, resulting in alteration of its pharmacokinetics. The first step in DCA metabolism is conversion to glyoxylate catalyzed by glutathione transferase zeta 1 (GSTZ1), for which DCA is a mechanism-based inactivator. The rate of GSTZ1 inactivation by DCA is influenced by age, *GSTZ1* haplotype and cellular concentrations of chloride. The effect of DCA on its own metabolism complicates the selection of an effective dose with minimal side effects.

Contents

1. Introduction

Dichloroacetate (DCA) is an intriguing small molecule. The pharmacological properties of dichloroacetic acid, its salts and derivatives have been investigated for almost a century. From the 1950s–1960s, diisopropylammonium dichloroacetate (DIPA) and other salts or ionic complexes of DCA were investigated experimentally and clinically for diverse indications, with little insight into how or where they acted (Stacpoole, 1969). Among the more intriguing properties of DIPA was its ability to lower blood glucose levels in rats with chemically-induced diabetes, but not in non-diabetic animals (Lorini & Ciman, 1962), a property subsequently found to be due solely to the DCA

* Corresponding author at: Department of Medicinal Chemistry, 1345 Center Drive, PO Box 100485, University of Florida, Gainesville, FL 32610-0485, United States. Tel.: +352 273 7707; fax: +352 392 9455.
E-mail address: mojames@ufl.edu (M.O. James).

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anion (Stacpoole & Felts, 1970). During the 1970s–1980s, the metabolic effects of DCA as the sodium salt were studied extensively and its primary sites and mechanisms of action were established (Stacpoole, 1989). The first human pharmacokinetic study of DCA was conducted in the 1980s and showed that DCA elimination was slowed substantially after multiple doses (Curry et al., 1985). It was subsequently shown that the major pathway of primary metabolism of DCA was conversion to glyoxylate (James et al., 1998), catalyzed by glutathione transferase zeta 1 (GSTZ1) (Tong et al., 1998a) and that this enzyme could be irreversibly inactivated by DCA (Anderson et al., 1999), a property that led to the prolongation of the elimination half-life following multiple doses (Curry et al., 1985; Stacpoole et al., 1998a; Schultz et al., 2002). This article will discuss the pharmacology, therapeutic applications, toxicology, pharmacokinetics and biotransformation of DCA in people and animal models.

2. Mechanism of action of dichloroacetate in mitochondria

Although DCA exerts clinically significant effects on lipid and lipoprotein metabolism (Stacpoole et al., 1978; Moore et al., 1979; Stacpoole et al., 1983c), most research has focused on its ability to modulate carbohydrate metabolism at the level of the mitochondrial pyruvate dehydrogenase complex (PDC).

The PDC is a multienzyme complex located in the mitochondrial matrix and performs the gatekeeper role of linking cytoplasmic glycolysis to the mitochondrial tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) as shown in Fig. 1. The reaction is rate-limiting for the aerobic oxidation of glucose and pyruvate and for other 3-carbon molecules (alanine, lactate) in equilibrium with pyruvate. Rapid regulation of the nuclear DNA-encoded PDC is mediated post-transcriptionally by reversible phosphorylation of 3 serine residues on the alpha subunit of the E1 (pyruvate dehydrogenase) component of the complex (E1α), in which the phosphorylated form is catalytically inactive (Patel & Korotchkina, 2006). Humans possess 4 isoforms of pyruvate dehydrogenase kinase (PDK 1–4), which inhibit the complex, and 2 isoforms of pyruvate dehydrogenase phosphatase (PDP 1 and 2), which maintain PDC in its unphosphorylated, active state. Both PD kinases and phosphatases are differentially expressed in tissues and are themselves highly regulated proteins (Bowker-Kinley et al., 1998). In general, PDC undergoes feedforward stimulation and feedback inhibition that is mediated *via* changes in PDK activity or expression. Thus, accumulation of the PDC reaction products, acetyl CoA and NADH, or the end product of OXPHOS, ATP, increase PDK activity and suppress PDC through phosphorylation at one or more serine residues on E1α. In contrast, the substrates for the PDC reaction inhibit PDKs and maintain or restore PDC activity.

DCA, a structural analog of pyruvate, is taken up by cells by the monocarboxylate transporter system (Jackson & Halestrap, 1996) and by the highly efficient sodium-coupled monocarboxylate transport, also called solute carrier family-5 member 8 (SLC5A8) transporter (Babu et al., 2011) and gains access to the mitochondrial matrix by the mitochondrial pyruvate transporter system (McCommis & Finck, 2015). DCA stimulates PDC activity by binding to the pyruvate binding site in the PDK N-terminal regulatory R domain, according to the co-crystallization structural data obtained for the PDK1-DCA and PDK2-DCA complexes (Knoechel et al., 2006; Kato et al., 2007). DCA binding at this site results in inhibition of PDK activity such that PDC remains in the active form. An oral dose of DCA is rapidly absorbed and widely distributed within minutes of administration (Stacpoole, 2011). It readily crosses the blood–brain barrier and can be measured in cerebrospinal fluid. Blood lactate concentrations begin to fall within about 15–30 min following oral or parenteral dosing and are a useful biomarker of DCA's action on PDC.

3. Therapeutic uses of dichloroacetate

3.1. Diabetes mellitus

Many acquired and genetic diseases, as well as nutritional perturbations, transcriptional factors and xenobiotics can also affect PDC activity by modulating the expression of one or more PDK isoforms. For example, conditions such as starvation, high fat diets and diabetes mellitus elevate circulating levels of free (unesterified) long chain fatty acids. The resultant increase in their mitochondrial beta-oxidation increases intra-mitochondrial ratios of acetyl CoA:CoA and NADH:NAD, leading to increased PDK activity and down-regulation of PDC (Randle et al., 1963; Hue & Taegtmeyer, 2009). The selective glucose-lowering action of DCA in diabetic, but not in healthy, animals was associated with

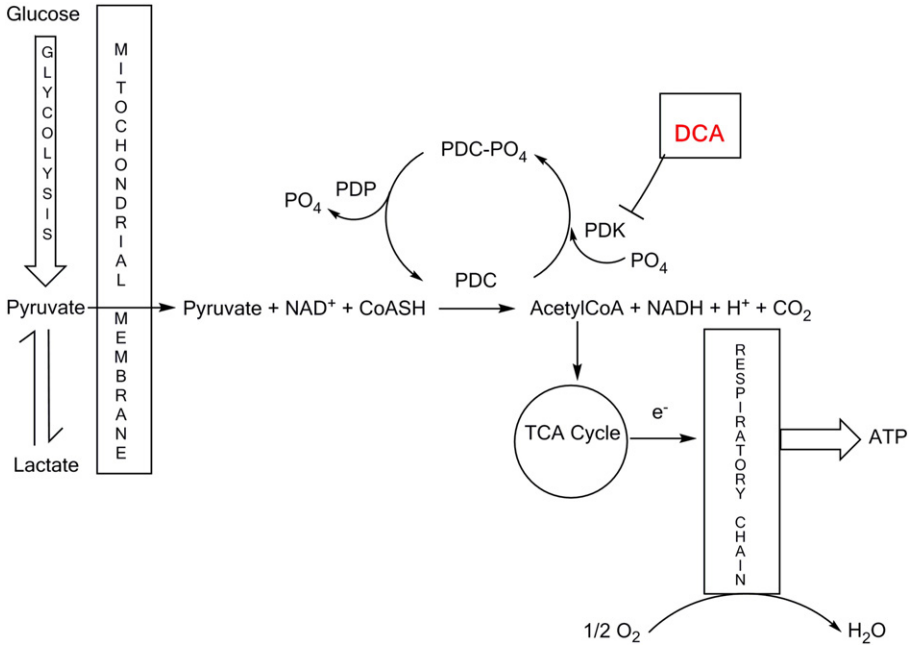

Fig. 1. Role of the pyruvate dehydrogenase complex in intermediary metabolism and site of action of DCA. PDC-PO_4 is the inactive phosphorylated form of pyruvate dehydrogenase complex; PDC is the active unphosphorylated form. PDK is pyruvate dehydrogenase kinase; PDP is pyruvate dehydrogenase phosphatase; e^- represents transfer of an electron.