ABSTRACT

Thiazolidinedione (TZD) drugs (Takeda Pharmaceuticals and Metabolic Solutions Development Company) targeting inhibition of the mitochondrial pyruvate carrier (MPC) are currently being tested in clinical trials to prevent progression into mild cognitive impairment of Alzheimer’s disease (AD) or in the pipeline to prevent neurodegeneration in Parkinson’s disease (PD). These have Ki values in the µM range. This study was focused on identifying candidate drug precursors of the natural cinnamic acid products that might have good bioavailability in the nM ranges forming covalent thiol bonds with targets. In silico protein homology modeling and ligand docking has demonstrated that binding cysteine residues within the transport channel is a key part of the inhibitory mechanism. These are covalent thiohemiacetal bonds with the alpha-carbon, carboxylate group, off a phenol ring. Like the classic MPC inhibitors, these natural derivatives of hydroxycinnamic acid have a conjugated pi-system used to form thiol bonds with the cysteine residue via Michael addition.
INTRODUCTION

The 3-carbon metabolite, pyruvate, is a major substrate for energy production in the mitochondrion where it is converted into acetyl-coenzyme A by the pyruvate dehydrogenase complex. In 2012, a family of mitochondrial pyruvate carrier (MPC) membrane proteins were characterized (Herzig et al., 2012). These transporters were shown to carry pyruvate across the inner mitochondrial membrane. As a novel drug target, inhibition of the MPCs by thiazolidinedione (TZD) (Divakaruni et al., 2013) drugs is being tested for the prevention of mild cognitive impairment from Alzheimer’s disease and the prevention of neurodegeneration from Parkinson’s disease (Divakarini et al., 2017; Ghosh et al., 2016; Shah et al., 2014); see also a companion paper in this issue (Phelix, Bourdon, Dugan, Villareal, & Perry, 2017). Since the standard control MPC inhibitors, used in validation studies of the novel MPC inhibitors, are cyano-derivatives of a synthetic form of cinnamic acid, we were curious why no one has ever tested any of the natural cinnamic acid compounds for MPC inhibition. Relative to Alzheimer’s disease we are also interested in the numerous natural derivatives that have potent anti-oxidant properties, since a key research focus has been on oxidative stress as the earliest measurable events in progression of this disease (Hammack, Perry, LeBaron, Villareal, & Phelix, 2015; Nunomura et al., 2001; Sayre, Smith, & Perry, 2001). Interestingly, caffeic acid phenethyl ester (2-phenylethyl (2E)-3-(3, 4-dihydroxyphenyl) acrylate, CAPE; also, a natural product from cinnamic acid) has been shown to prevent dementia in rats that had received intracerebroventricular streptozotocin (Kumar, Kaur, & Bansal, 2017).

The original inhibitors of mitochondrial pyruvate transport arose from analogues of the enol form of pyruvate actually intended to inhibit enzymes for pyruvate metabolism. The most potent transport inhibitors turned out to be derivatives of cinnamic acid with electron withdrawing groups promoting Michael addition reactions with cysteine residues in the MPC channel, i.e., α-cyanocinnamic acid and α-cyano-4-hydroxycinnamate (Halestrap, 1978; Halestrap & Denton, 1974; Nałęcz, Müller, Zambrowicz, Wojtczak, & Azzi, 1990). Later more potent inhibitors were developed with emphasis on the α-cyanopropenoate group and a hydrophobic aromatic side chain, e.g., α-cyano-β-(2-phenylindol-3-yl) acrylate (UK-5099) the most potent cinnamic acid derivative in micromolar (µM) ranges (Halestrap, 1975, 1978); or discovered as even more potent nanomolar range inhibitors as thiazolidine compounds, i.e., GW604714X and GW450863 (Hildyard, Ämmälä, Dukes, Thomson, & Halestrap, 2005). These drugs were rarely used for tissue or in vivo studies due to poor bioavailability attributed to both inhibition of the monocarboxylate transporter (MCT) and binding to albumin (Halestrap & Denton, 1975). Intestinal MCT is critical for absorption of many types of drugs and compounds for adequate oral bioavailability (El-Kattan, 2017). When they have been used for in vivo testing, large doses had to be administered via the intraperitoneal route due to binding to plasm proteins and lower potency for inhibiting MCT versus MPC (Granja et al., 2013; Patterson et al., 2014; Zhang et al., 2016). However, modifications of α-cyanocinnamic acid that greatly increased potency as MCT inhibitors, did not diminish oral bioavailability once sodium salt compounds were developed (Gurrapu et al., 2015) and it is not known if such modifications equally increase potency for MPC inhibition. Actually, all these in vivo studies neglect potential involvement of MPC inhibition in the focus of the experimental designs. Oddly, natural derivatives of cinnamic acid have not been tested directly for MPC inhibition (Adisakwattana, 2017; Alam et al., 2016; Ruan et al., 2014). Ferulic acid was shown to bind human MPC2 subunit using homology modeling and in silico molecular docking analyses (Otero, Papadakis, Gupta Udatha, Nielsen, & Panagiotou, 2010) and chlorogenic acid was shown to inhibit pyruvate oxidation in cardiac mitochondria (Bernatoniene et al., 2014). Chlorogenic acid has recently been reported, in a retrospective meta-analysis, to have positive...
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