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Aldo-keto reductases (AKR) from the AKR1C subfamily catalyze the carbonyl reduction of the novel anticancer drug oracin in man

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Abstract

In many cases, cancer chemotherapy still obtains unsatisfactory response rates, rare complete remissions and responses of relatively short duration. Therefore, more effective drugs with new structures against cancer are continuously sought. Oracin, 6-[2-(2-hydroxyethyl)-aminoethyl]-5,11-dioxo-5,6-dihydro-11*H*-indeno[1,2-*c*]isoquinoline, is a new anticancer drug which is presently in phase II clinical trials. Pharmacokinetic studies have revealed that oracin undergoes metabolic inactivation by carbonyl reduction. Since metabolic inactivation contributes to chemotherapy resistance, detailed knowledge about the participating enzymes is necessary. In the present study, we identified three members of the aldo-keto reductase (AKR) superfamily to mediate oracin carbonyl reduction in man. For AKR1C1, 1C2 and 1C4, purified from human liver cytosol, we could determine the kinetics and catalytic efficiencies. In addition, we investigated the stereospecificity of formation of reduced oracin (DHO). Whereas AKR1C2 and 1C4 are exclusively (100%) stereospecific for (+)-DHO formation, some 3% of (−)-DHO formation was found for AKR1C1. On the other hand, the activity of AKR1C1 in overall oracin reduction was one order of magnitude higher compared to AKR1C2 and 1C4. Detailed knowledge about all enzymes involved in oracin detoxification may help to improve an anticancer regimen by co-application of respective inhibitors.
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Keywords: Aldo-keto reductases (AKR); Drug metabolism; Biotransformation; Carbonyl reduction; Stereospecificity; Chemotherapeutics; Oracin

1. Introduction

Resistance to anticancer drugs and organ specific toxicity are two of the major problems in chemotherapy. For example, anthracyclines such as daunorubicin and doxorubicin undergo carbonyl reduction as an undesired metabolic pathway, since the resulting secondary alcohol metabolites daunorubicinol and doxorubicinol, respectively, are less active in terms of anti-tumor activity. In addition, these metabolites are responsible for the life-threatening cardiac toxicity that limits the clinical use of the parent drugs (Ax et al., 2000; Jin and Penning, 2007).

The search for more effective drugs against cancer has resulted in compounds with new structures. Oracin, 6-[2-(2-hydroxyethyl)-aminoethyl]-5,11-dioxo-5,6-dihydro-11*H*-indeno[1,2-*c*]isoquinoline, is one of these prospective anticancer drugs, presently in phase II clinical trials. From its chemical structure, a DNA intercalation mode of action can be inferred, similar to that of anti-tumor antibiotics from the anthracycline group. However, the wide spectrum of tumors that are sensitive

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to oracin does not only result from this single mechanism of action, which manifests itself by an inhibition of DNA and RNA synthesis, followed by a decrease in protein content in tumor cells (Melka, 1993). Several other mechanisms affecting tumor cell growth have been demonstrated. They involve the inhibition of topoisomerase II (EC 5.99.1.3) which was isolated from nuclei of Ehrlich ascites carcinoma cells (Miko et al., 2002), the stimulation of aerobic consumption of glucose and, to a lesser extent, of formation of lactate in tumor cells, as well as induction of apoptosis (Melka, 1993).

The main advantages of this novel chemotherapeutic are the possibility of oral administration, the above-mentioned combination of different anti-tumor mechanisms, the absence of cardiotoxicity (Gersl et al., 1996) (which e.g. is the main dose-restricting factor in clinical chemotherapy of doxorubicin), the negative results in the Ames test on mutagenicity (Marhan, 1995), very low hepatotoxicity, and its favorable pharmacokinetics.

In view of its promising biological activities in chemotherapy and favorable pharmacokinetic properties, the biotransformation of oracin is being intensively studied. Metabolic studies have revealed carbonyl reduction of oracin to dihydrooracin (DHO) as the main metabolic pathway in common laboratory animals (Szotakova et al., 1996; Wsol et al., 1996, 1998) as well as in human liver (Wsol et al., 2000). Reduction of the pro-chiral carbonyl group at the 11-position of oracin (Fig. 1) leads to the formation of chiral DHO. It was found that DHO is stereospecifically formed both in microsomal and cytosolic fractions of all species studied and the stereospecificity is also affected by gender of the laboratory animals (Wsol et al., 1999).

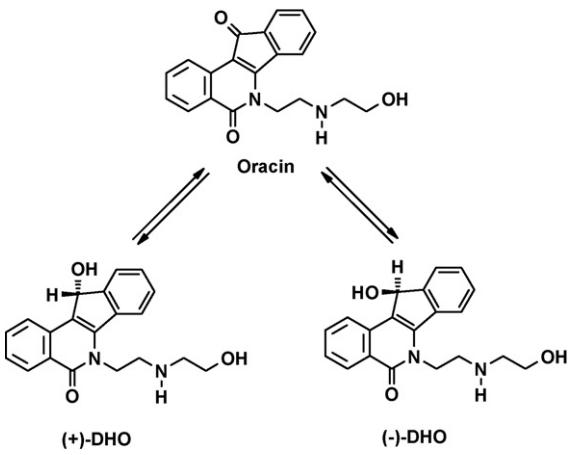

Fig. 1. Metabolic conversion of the pro-chiral anticancer drug oracin to its DHO enantiomers.

Carbonyl reduction is an important process within the cell and can be regarded as phase I biotransformation reaction that leads to the inactivation and elimination of xenobiotic substances including drugs and toxicants. Like oxidation reactions via the cytochrome P450 system which usually results in a more hydrophilic functional group within a lipophilic molecule, carbonyl reduction of ketones and aldehydes leads to secondary or primary alcohols, respectively, that facilitate their elimination.

Many different enzymes have been identified that catalyze the carbonyl reduction of xenobiotics. Most of them exhibit pluripotency in that they also reduce a variety of endogenous compounds, including sugars, prostaglandins, retinoids and steroids (Hoffmann and Maser, 2007; Jin and Penning, 2007; Matsunaga et al., 2006; Oppermann, 2007; Rosemond and Walsh, 2004). Based on their primary structure, these pluripotent carbonyl reducing enzymes have been grouped into two large protein superfamilies, the short-chain dehydrogenases/reductases (SDR) (Jörnvall et al., 1995) and the aldo-keto reductases (AKR) (Jez et al., 1997).

On the basis of induction and inhibition studies with whole microsomal fractions it was found that 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD 1) (EC 1.1.1.146) from the SDR superfamily seems to participate in oracin carbonyl reduction on the microsomal level in rat liver (Szotakova et al., 2000). Later studies on purified 11β-HSD 1 from mouse liver (Wsol et al., 2003) and from human liver (Wsol et al., 2004) have revealed that this enzyme plays the key role in carbonyl reduction of oracin in microsomes.

In the present paper, we have found that AKRs from the AKR1C subfamily catalyze oracin carbonyl reduction in human liver cytosol. AKRs are soluble NAD(P)(H) dependent oxidoreductases that are evolutionary conserved from bacteria to humans (Hyndman et al., 2003; Jez et al., 1997). The majority of AKRs are monomeric proteins of 34–37 kDa with a characteristic $(\alpha/\beta)_8$ TIM barrel structure. There are currently more than 140 members in the AKR superfamily, which is divided into respective families and subfamilies (Hyndman et al., 2003; Jez et al., 1997). Recently, a website on the AKRs has been constructed at http://www.med.upenn.edu/akr. The human genome project (HUGO) has identified 10 human AKR enzymes, of which the four members of the AKR1C subfamily, AKR1C1–AKR1C4 exhibit pluripotency for endogenous steroids and non-steroidal xenobiotic carbonyl compounds.

Since carbonyl reduction of a pro-chiral centre may lead to the formation of two different enantiomeric alcohol metabolites, the stereospecificity of the reductases in

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