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Chemico-Biological Interactions 162 (2006) 31–42
Chemico-Biological Interactions
www.elsevier.com/locate/chembioint

Acute effects of novel selenazolidines on murine chemoprotective enzymes

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Received 17 March 2006; received in revised form 5 May 2006; accepted 5 May 2006
Available online 12 May 2006

Abstract

Novel selenazolidines, designed as L-selenocysteine prodrugs and potential cancer chemopreventive agents, were examined for their ability to affect the transcription of murine hepatic chemoprotective enzymes. Compounds investigated were selenazolidine-4(*R*)-carboxylic acid (SCA) and six 2-substituted derivatives that cover a *C* log *P* range of −0.512 to −3.062. Their biological effects were compared with those of L-selenocystine. Gene transcripts were examined 24 h after a single dose, administered i.p. and i.g., and covered a range of chemoprotective enzymes; alpha, mu and pi class glutathione transferases (Gsts), UDP-glucuronosyltransferases (Ugts) 1a1, 1a6, 1a9, and 2b5, glutathione peroxidase 1 (Gpx), thioredoxin reductase (Tr), NAD(P)H-quinone oxidoreductase 1 (Nqo), and microsomal epoxide hydrolase (Meh). When given i.g., 2-butyl SCA (BSCA) resulted in elevations in alpha, mu and pi class Gsts, Ugt1a6, Tr, and Gpx, and 2-phenyl SCA (PhSCA) elevated GstP, Ugt1a9, Tr, Gpx (3 kb), and Meh. Other derivatives with *C* log *P* values both lower [2-(2′-hydroxy)phenyl SCA (PhOHSCA) and 2-methyl SCA (MSCA)] and higher [2-cyclohexyl SCA (ChSCA) and 2-oxo SCA (OSCA)] than BSCA and PhSCA elevated far fewer transcripts; PhOHSCA (Ugt1a1, Gpx), MSCA (Ugt1a1, Meh), ChSCA (Ugt1a1, Ugt1a9), and OSCA (Ugt1a6, Ugt1a9, GstM). When given i.p., the most pervasive transcript changes were parallel increases in Nqo and Tr transcripts which occurred with BSCA, PhSCA, MSCA, and OSCA. PhSCA also increased GstP, and PhOHSCA increased Ugt1a1 and Ugt1a6 levels. Unique among the compounds, PhSCA reduced the transcript levels of GstA, and the 1.6 kb transcript of Gpx although only when given i.p. Neither L-selenocystine nor SCA affected the level of any transcript and no compound altered the amount of Ugt2b5 mRNA. Despite chemical similarity and common ability to potentially serve as a source of L-selenocysteine, each selenazolidine compound appeared to elicit a unique pattern of mRNA responses and by either route of administration, there was no correlation between the magnitude of response of any gene and the calculated *C* log *P* values of the organoselenium compounds.

Keywords: Selenium; Selenocysteine prodrugs; Selenazolidines; Mouse; mRNA; Thioredoxin reductase; Glutathione peroxidase; NAD(P)H-quinone oxidoreductase; Glutathione transferases; UDP-glucuronosyltransferases; Microsomal epoxide hydrolase

1. Introduction

For more than four decades selenium has been categorized as an essential mammalian micronutrient. Although selenium and selenium-containing compounds provide protection against many degenerative conditions, including cancer, the mechanism or mechanisms

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doi:10.1016/j.cbi.2006.05.002

by which this occurs continues to require investigation. In chemoprevention against cancer, an effect related to the maintenance or enhancement of "protective" enzymes is commonly invoked. Protective enzymes include the selenoproteins glutathione peroxidase (GPx) and thioredoxin reductase (TR), quinone oxidoreductase (NQO), as well as UDP-glucuronosyltransferases (UGTs), microsomal epoxide hydrolase (mEH) and glutathione transferases (GSTs). All are involved in either sequestering reactive oxygen species and reactive electrophilic metabolites or maintaining cellular components in their appropriate redox status.

In the study of selenium and selenium compound efficacy in chemoprevention, naturally occurring compounds have not always shown convincing and comprehensive activity. Inorganic selenite, in a variety of dosing regimens but centered around a selenium dose level of around 5 ppm, was not effective against 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced rat mammary tumors [1], 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced mouse lung tumors [2,3] or azaserine-induced rat pancreatic and hepatic neoplasms [4]. However, selenite at similar dose levels, was effective against DMBA-induced mammary tumors in mice [5] and rats [6–8], although only weakly so [9]. Of the selenium-containing amino acids and their derivatives, selenocystine at selenium dose levels of 2 and 3 ppm was not effective against DMBA-induced mammary tumors in mice [5], and only weakly effective [9], or not effective [10] in rat, whereas in mice, and at 15 ppm, it was effective for NNK-induced lung tumors [3]. Selenomethionine at selenium dose levels of 2–4 ppm was not effective against DMBA-induced mammary tumors in mice [5] and only weakly effective against DMBA-induced mammary tumors in rat [9] and NNK-induced lung tumors in mice [3]. Modified seleno-amino acids, Se-methyl-, Se-propyl-, and Se-allylselenocysteines were effective against DMBA and *N*-methyl-*N*-nitrosourea (MNU)-induced mammary tumors in rat [10–12] but Se-methylselenocysteine at similar dose levels (3 ppm) was not effective against NNK-induced lung tumors in mice [3].

In the search for more consistently efficacious compounds, several organoselenium compounds particularly organoselenocyanates have been created and evaluated, although again with a variety of dosing regimens that makes direct efficacy comparisons difficult. In general, these compounds have been investigated at much higher selenium dose levels (up to 40 ppm) than was possible with inorganic selenite. Benzylselenocyanate was effective against benzo[*a*]pyrene-induced mouse forestomach tumors [13], azoxymethane-induced rat liver tumors [14] and DMBA-induced rat mammary tumors [1]. 1,4-Phenylenebis(methylene) selenocyanate (*p*-XSC) also had wide ranging efficacy against tumors induced by a variety of carcinogens in many tissues; in rat colon after azoxymethane [15], in rat mammary tissue after DMBA [16], in mouse lung after NNK [2,17–20], and in rat tongue after 4-nitroquinoline-1-oxide [21]. It was also effective against spontaneous familial adenomatous polyposis development in APC(min) mice [22]. The di-glutathione conjugate of *p*-XSC was also effective against azoxymethane-induced tumors in rat colon [23]. Aliphatic rather than aromatic selenocyanates have also proved effective against DMBA-induced rat mammary tumors [24].

Organoselenium compounds in addition to selenocyanates have been investigated, mostly with rat mammary tumor models and have met with varying degrees of efficacy. Methylphenylselenide, *p*-xylylbis(methylselenide), triphenylselenonium chloride, and diphenyl selenide were investigated against MNU-induced tumors [25], and triphenylselenonium chloride and diphenyl selenide against DMBA-induced tumors [26,27]. Early studies with *p*-methoxybenzeneselenol had found it to be effective against benzo[*a*]pyrene-induced mouse forestomach tumors [13] and azoxymethane-induced rat liver tumors [28].

Of all the organoselenium compounds developed and evaluated, few have been examined for the changes they elicit in chemoprotective enzymes, and where such studies have been undertaken, most have examined activities of only one or two, most commonly including GSTs. Most of these changes were investigated after several months of organoselenium compound administration, with only a couple of studies evaluating changes after a week, and none after just one or a few days. Recently, elevated GST activity was reported in mouse liver, skin, and colon following diphenylmethylselenocyanate administration [29,30]. In earlier studies, GSTM activity was increased in colon mucosa of azoxymethane-treated rats after 10 weeks of dietary exposure to the glutathione conjugate of benzylselenocyanate [31]. With long-term administration of *p*-XSC to otherwise naïve animals, no elevation of rat liver GST (1-chloro-2,4-dinitrobenzene, CDNB) activity was seen [21]. However, in a 1-week study with lower *p*-XSC concentrations, increased GST (CDNB) activity in liver, lung and kidney but not colon or mammary tissue was reported [32]. Utilizing class-selective substrates, GSTA activity was increased only in lung, and GSTP activity in lung and colon [32]. No GST class-selective substrate activity was statistically increased in liver. In a similar study in mice,