Available online at www.sciencedirect.com
SCIENCE DIRECT®
Mutation Research 589 (2005) 47–65
Reviews in Mutation Research
www.elsevier.com/locate/reviewsmr
Community address: www.elsevier.com/locate/mutres

Review

Bile acids as carcinogens in human gastrointestinal cancers

H. Bernstein[a,b], C. Bernstein[a,*], C.M. Payne[a,b], K. Dvorakova[a,b], H. Garewal[b,c,d]

[a]*Department of Microbiology and Immunology, College of Medicine, University of Arizona, Tucson AZ 85724, USA*
[b]*Arizona Cancer Center, University of Arizona, Tucson, AZ 85724, USA*
[c]*Department of Internal Medicine, Arizona Cancer Center, College of Medicine, University of Arizona, Tucson AZ 85724, USA*
[d]*Tucson Veterans Affairs Medical Center, Section of Hematology/Oncology, Tucson, AZ 85723, USA*

Received 26 January 2004; received in revised form 27 July 2004; accepted 6 August 2004
Available online 22 September 2004

Abstract

Bile acids were first proposed to be carcinogens in 1939 and 1940. On the basis of later work with rodent models, bile acids came to be regarded as cancer promoters rather than carcinogens. However, considerable indirect evidence, obtained more recently, supports the view that bile acids are carcinogens in humans. At least 15 reports, from 1980 through 2003, indicate that bile acids cause DNA damage. The mechanism is probably indirect, involving induction of oxidative stress and production of reactive oxygen species that then damage DNA. Repeated DNA damage likely increases the mutation rate, including the mutation rate of tumor suppressor genes and oncogenes. Additional reports, from 1994 through 2002, indicate that bile acids, at the increased concentrations accompanying a high fat diet, induce frequent apoptosis. Those cells within the exposed population with reduced apoptosis capability tend to survive and selectively proliferate. That bile acids cause DNA damage and may select for apoptosis-resistant cells (both leading to increased mutation), indicates that bile acids are likely carcinogens. In humans, an increased incidence of cancer of the laryngopharyngeal tract, esophagus, stomach, pancreas, the small intestine (near the Ampulla of Vater) and the colon are associated with high levels of bile acids. The much larger number of cell generations in the colonic (and, likely, other gastrointestinal) epithelia of humans compared to rodents may allow time for induction and selection of mutations leading to cancer in humans, although not in rodents.

Keywords: Bile acids; Carcinogen; Apoptosis; Gastrointestinal cancer; DNA damage; Oxidative stress

Contents

* Corresponding author. Tel.: +1 520 626 6069; fax: +1 520 626 2100.
E-mail address: bernstein3@earthlink.net (C. Bernstein).

1383-5742/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.mrrev.2004.08.001

1. Introduction

The bile acid, deoxycholic acid, was first proposed to be a carcinogen in 1940 by Cook et al. [1], based on induction of tumors in mice when injected, in their flanks, with this bile acid. These authors also cite a 1939 meeting report by Vittorio Ghiron that ‘‘desoxycholic acid elicited transplantable subcutaneous fibro-sarcomas in a high proportion of the mice and rats injected. This is believed to be the first experimental production of malignant growths with a compound that exists under some conditions in the human body.’’ In a 1999 mouse experiment, using mice with a germ line mutation in *Apc* (Min/+) as a model of familial adenomatous polyposis, administration of chenodeoxycholate increased duodenal tumors [2]. This increase occurred without addition of a standard carcinogen such as MNNG, MNU or azoxymethane, so that in Min/+ mice, the bile acid chenodeoxycholate was a carcinogen.

In a number of rat experiments reported between 1974 and 1993, several bile acids were shown to be promoters, increasing tumorigenesis by known carcinogens. However, the bile acids, by themselves, were not carcinogens, failing to induce colon tumors. In particular, in rats, the bile acids lithocholic, taurodeoxycholic and deoxycholic acids had a promoting effect on colon carcinogenesis after intrarectal instillation of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) [3–5]. The bile acid, cholic acid, also had a promoting effect on colon tumor formation in rats after intrarectal instillation of *N*-methyl-*N*-nitrosourea (MNU) [6] or subcutaneous injection of azoxymethane [7]. The promoting effect of cholic acid may have been due to the formation of deoxycholic acid from cholic acid by bacterial action in the colon [8]. Further, taurocholate, in rats, enhanced the induction by MNNG of hyperplastic and neoplastic lesions in stomach mucosa [9]. Based largely on these experiments in non-mutated rat model systems, it has been generally assumed that bile acids act as promoters, but not as carcinogens, in humans.

Recently, however, considerable indirect evidence and logical argument supports the view that bile acids are carcinogens in humans. The evidence and arguments are detailed below, and include evidence