Bile Acids

Bile acids research has gone through many stages, beginning with the determination of the structure of bile acids and the characterization of their surface-colloidal and detergent properties. More recently, there has been considerable interest in the structural modification of common bile acids and the syntheses of their artificial congeners and derivatives. Although intensive research in the area has already extended over several decades, the toxicology and bioactivity of bile acids is still a focus of great interest, as there is growing evidence that bile acids, or at least some of them, can be involved in carcinogenesis and other malignant changes. The new book *Bile Acids: Toxicology and Bioactivity*, edited by Gareth Jenkins (Institute of Life Science, School of Medicine, Swansea University) and Laura Hardie (Molecular Epidemiology Unit, University of Leeds) is focused mainly on pathological functions of bile acids. The book consists of eight chapters written by different world experts in the field.

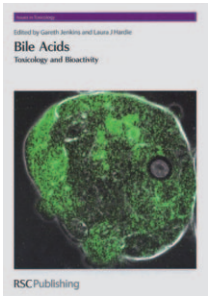
The first chapter, an overview of the synthesis, chemistry, and function of bile acids, by Dennis Stamp and Gareth Jenkins, gives basic knowledge about the biosynthesis of bile acids and their amino-acid conjugation. This chapter also includes a short description of bile acid and cholesterol receptors. Some basic features of the chemistry and biochemical properties of common bile acids are also described. At the end of the chapter the authors mention some therapies for the deleterious effects of bile acids. Although this chapter contains some evident deficiencies in describing the stereochemistry of common bile acids (ring fusions in the perhydrocyclopentanophenanthrene skeleton and the orientation of hydroxy groups), this is not a very serious drawback because the knowledge is available elsewhere, and beginners are unlikely to use this book as their first journey into bile acids.

Chapter 2, on bile-acids physiology and measurements, written by Peter E. Ross, gives a detailed description of the role of enterohepatic circulation: the transport of protein-bound bile acids in blood and their efficient removal therefrom by hepatocytes. Functions and specificity of the protein transporters NTCP and OATP are included, as well as the regulation of their expression. Next the author describes the transport of bile acids across the hepatocyte and the export of bile acids therefrom by BSEP and other transporters. That is followed by a description of bile and water secretion, as well as functions of cholangiocytes, the gall-bladder, the small bowel, and the intestine. The absorption of conjugated bile acids from the small bowel terminal lumen proceeds efficiently with ASBT, while non-conjugated bile acids may be absorbed passively. Two last steps in enterohepatic circulation are the transport across the enterocyte and export into portal blood. In spite of the efficiency of these processes, about 5 % of the bile acids pool enters the colon, where it is extensively attacked by the microbial population causing de-conjugation and oxidation of the hydroxyl groups. This leads to the formation of secondary bile acids, deoxycholic and lithocholic acids, which are major bile acids in feces. At the end of this chapter is a description of how to measure bile acids. Their separation is achieved by extraction, which is usually followed by assays based on 3α-hydroxysteroid dehydrogenase to form 3-keto bile acid. Methods based on GLC, HPLC, and radio-immunoassay are also mentioned briefly. The only drawback in this longest chapter of the book is that it does not contain a summary or conclusions, unlike other chapters of the book.

Chapter 3, by Katerina Dvorak, Harris Bernstein, Claire M. Payne, Carol Bernstein, and Harinder Gareval, deals with bile-acid function and apoptosis in relation to gastrointestinal cancer, and begins by identifying the target organs/tissues/cells where certain bile acids cause apoptosis. That is followed by a list of different kinds of cancers, such as those of the esophagus, stomach, pancreas, liver, small intestine, and colon, with evidence about their association with different bile acids. The general mechanism in all cases is believed to be oxidative/nitrosative stress and DNA damage in cells of the gastrointestinal tract. It is also known that unrepaired DNA damage can trigger apoptosis. Repeated exposure to high concentrations of bile acids can target apoptosis-resistant cells in the gastrointestinal tract leading to increased mutation. The authors consider that, in humans as distinct from short-term rodent models, bile acids can act as carcinogens when there is repeated exposure to high levels over several decades.

Chapter 4, by Laura J. Hardie, deals with genotoxicity of bile acids. It has long been known that bile acids are potential carcinogens. However, the recent findings from research on rat models indicate that bile acids can increase the effects of other carcinogens. Also, bile acids alone seem to have promoting effects during tumor initiation. Among bile acids, deoxycholic acid, DCA, has significant genotoxic effects that could contribute to tumor initiation. In the context of reflux disease, the genotoxicity of this secondary bile acid in both acidic and neutral conditions could explain the rise of the incidence of oesophagal adenocarcinoma, despite the widespread use of acid-depressing medication.

In Chapter 5, Mark A. Hull discusses the connection between bile acids and colorectal cancer. As in Chapter 4, here again secondary



Toxicology and Bioactivity. Edited by Gareth J. Jenkins and Laura J. Hardie. Royal Society of Chemistry, Cambridge 2008. 176 pp., hardcover £59.95.—ISBN 978-0854048465

bile acids and especially DCA are believed to play a role in human colorectal carcinogenesis. However, it is difficult to measure the relative significance of the bile acids compared with other genetic and environmental factors. Among therapeutic bile acids, ursodeoxycholic acid, UDCA (the 7β-hydroxy epimer of chenodeoxycholic acid, separated from bear bile) has been shown to possess anti-neoplastic activity in ulcerative colitis-associated colorectal carcinogenesis. Furthermore, UDCA has an excellent safety profile compared with other candidate chemo-prevention agents. The last sentence of this chapter: "The development of lipophilic bile-acid-drug conjugates and other bile acid derivatives is an important advance with exciting therapeutic possibilities", is a very important argument regarding the use of bile acids as components of pro-drugs and other therapeutic agents. This could be a topic of a review article in the near future.

Chapter 6, by Gareth Jenkins and James Cronin, focuses on the connection between bile acids and oesophagal adenocarcinoma, OA. It is caused by chronic gastro-oesophagal reflux disease. Again, UDCA seems to be the Good and DCA the Bad in this connection. The summary at the end of this chapter is very clear and contains six statements: 1) bile acids are centrally involved as carcinogens in OA; 2) screening of bile acids can serve as a biomarker of OA development; 3) acid suppression is probably responsible for deconjugation of bile acids causing oesophagal exposure to free bile acids; 4) acid suppression also promotes the activity of the most damaging subtypes of bile acids; 5) reactive oxygen species play a central role in bile-acid activity, and therefore antioxidant supplementation can be important; and 6) other forms of possible treatment include bile-acid sequestrants and UDCA.

Chapter 7, by Lucinda Summers and Laura J. Hardie, gives an interesting discussion of the link between bile acids and obesity, which is a global epidemic leading to an increase of morbidity and mortality. Traditionally, it has been thought that by increasing fat absorption bile acids can cause a greater risk of obesity. However, recent studies indicate that bile acids have a much wider role in the regulation of energy balance in the body. Bile acids are natural ligands for TGR5 and FXR receptors, and modulate adipocyte differentiation and function, thermogenesis, and glucose, lipid and insulin homeostasis (in addition to cholesterol homeostasis). These findings indicate the possibility of using dietary sequestration of bile acids and/or targeting of bile-acid signaling pathways to control obesity and other pathological conditions such as insulin resistance, impaired glucose tolerance, and dyslipidemia.

The last chapter, written by Linzi A. Thomas, is concerned with a more traditional topic in bile-acids research, namely the role of bile acids in cholesterol-rich gallstone formation, in which pathogenesis is multi-factorial. The precipitation and nucleation of cholesterol micro-crystals from supersaturated bile is a critical step in gall-stone formation. The "bad" bile is supersaturated with cholesterol, and has excess cholesterol in vesicles, rapid microcrystal nucleation times, and an increased percentage of DCA in bile, which has been argued to be one of the factors leading to cholesterol gall-stone formation.

As a whole, this book gives interesting new data on the toxicology and bioactivity of bile acids. It seems obvious, based on various evidence, that some bile acids, and especially deoxycholic acid, can cause malignant changes and are connected with several forms of cancer, in addition to the well-known effect of cholesterol-rich gall-stone formation. The eight chapters give eight different points of view, with contents that overlap to various extents. A short preface by the editors serves as an overview of the separate chapters, which have been written by world experts. This book could be especially useful for oncologists. A recent review article entitled "Bile Acids: Chemistry, Pathochemistry, Biology, Pathobiology, and Therapeutics" (A. Hofmann, L. Hagey, *Cell. Mol. Life Sci.* **2008**, *65*, 2461–2483) overlaps partly with this book in subject matter. The review article gives a more concise account of the pathology of bile acids, and therefore I can recommend the reading of both these sources to get an idea of the latest discoveries about bile acids and their multiple functions in mammals.

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DOI: 10.1002/anie.200805403