

Bile acids: developments new and very old

William C. Duane, *Associate Editor*¹

Department of Medicine, Veterans Affairs Medical Center and University of Minnesota, Minneapolis, MN 55417

With this issue of the *Journal of Lipid Research*, we begin a thematic review series focused on bile acids. The term "bile acid" was first coined in 1838 by Demarcay (1) to describe an acidic fraction of bile appreciated as early as 1807 (2). Since that time, an enormous amount of careful, often ingenious, work has brought us to our current understanding of this acid fraction of bile. The investigators who made these contributions are too numerous to name but the list includes many of towering scientific stature. Cumulatively, they have characterized these molecules in terms of chemical structure, physical chemistry, physiologic behavior, pathophysiological importance, and therapeutic usefulness.

Bile acids interest both basic scientists and clinicians for several reasons. First, they are quantitatively important products of cholesterol catabolism such that about half of cholesterol loss occurs via conversion to bile acids. Second, they play a central role both in absorption of dietary fat and solubilization of biliary cholesterol because of their amphiphilic character. Third, biliary secretion of bile acids serves to maintain bile flow and prevent cholestasis. Fourth, certain bile acids, most particularly ursodeoxycholic acid, have proven useful as therapeutic agents. Finally, a number of recent studies have demonstrated that bile acids play a fundamental role as regulatory molecules at the cellular level. This thematic review series will touch on all these central roles played by bile acids and explore avenues of investigation that have branched out from them.

For those of us who focused for years on the physiology and chemistry of bile acids, evidence that these molecules also functioned as signaling molecules was a surprising revelation. Although this area of study is less than 10 years old, it has already produced a body of work suggesting that bile acid signaling plays a regulatory role in a diverse variety of metabolic processes ranging from lipid homeostasis to glucose metabolism to energy expenditure. It is perhaps appropriate that we begin our series with a review of this newest of bile acid topics. The review was written by Dr. Philip Hylemon and coworkers, who have been at the forefront of much of this new work.

One of the critical cell regulatory processes activated by certain hydrophobic bile acids is apoptosis (3). Conversely,

the hydrophilic bile acid, ursodeoxycholic acid, and its taurine conjugate can elevate the apoptotic threshold, with the result that apoptosis induced by other bile acids or nonbile acid stimulators is prevented or diminished (4, 5). This effect is believed to be at least in part responsible for the beneficial effects of ursodeoxycholic acid in some cholestatic conditions, and interestingly, in some neurological diseases as well. Dr. Cecilia Rodrigues and coworkers will review this newly appreciated role of bile acids in the regulation of apoptosis.

Of course, the most obvious pathway regulated by bile acids is that of bile acid synthesis itself. That bile acids somehow regulated their own synthesis has been known for decades. However, the field was shaken in the early 1980s when the late Dr. Roger Davis and coworkers (6) reported that bile acids added to hepatocyte cultures did not inhibit bile acid production. Since then, a number of careful studies have defined the molecular mechanisms for regulation of bile acid synthesis and, more recently, have provided an explanation that reconciles the findings of Dr. Davis with known effects of bile acid administration and deprivation on bile acid synthesis (7). Dr. John Chiang will explore these intricacies and cover mechanisms of regulation unrelated to bile acids.

Some of the terminal steps in bile acid synthesis take place in peroxisomes, subcellular organelles first described in the late 1960s (8). A little over 10 years after the discovery of peroxisomes, the late Dr. Russell Hanson and coworkers (9) defined the metabolic defect in Zellweger's Syndrome to be the inability to cleave the three carbon side-chain of $3\alpha, 7\alpha, 12\alpha$ -trihydroxy- 5β -cholestanoic acid. Originally, the authors believed this defect to be in the mitochondria; however, it was soon shown to be in the peroxisome (10). Since that time, much has been learned about the role of peroxisomes in bile acid synthesis. Dr. Sacha Ferdinandusse and coauthors will provide a timely and informative review of this topic.


The enterohepatic circulation (EHC) is central to understanding functions of bile acids. Decades of study have yielded a relatively complete picture of the physiology of the EHC, including hepatic uptake, hepatic secretion, and intestinal absorption. More recently, molecular biology has provided the tools enabling definition of the transporters central to the EHC. Dr. Paul Dawson and coauthors will review the now extensive literature on these transporters of bile acid, both in the liver and intestine.

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For centuries, bear bile has been used in the Orient to treat a wide variety of conditions. Therapeutic use of bile acids in the West is, by comparison, much more recent. A pivotal study was that of Thistle and Hofmann (11), which reported dissolution of cholesterol gallstones by oral administration of chenodeoxycholic acid. Since that time, we have learned that ursodeoxycholic acid is a better option for treatment of cholesterol gallstones and, in addition, that ursodeoxycholic acid can be therapeutically useful for the treatment of some liver diseases. An enormous amount of work has been devoted to this subject. Dr. Ulrich Beuers will review the evidence for and against the efficacy of ursodeoxycholic acid in specific situations and discuss the mechanism by which these beneficial effects are achieved.

Our final two thematic reviews will be from two esteemed investigators who have spent long and productive careers studying bile acids. The first is Dr. Jan Sjovall, who has been publishing on bile acids for more than 50 years, often with a focus on analytic techniques. We will be the beneficiaries of his extensive experience, knowledge, and insight in a review, written by Dr. Sjovall and coauthors, which will update us on techniques for measuring bile acids in biological fluids. This monograph should be invaluable to investigators, particularly young investigators, whose studies require separation and quantitation of specific bile acids.

Lastly, few people can view the field of bile acids with the breadth and depth of Dr. Alan Hofmann. He could easily summarize the last half century of bile acid research, but in this series we have asked him instead to take a view over many millennia. He and his coauthors will provide perspective on the evolution of bile acids. Their extensive studies of bile acids in a wide variety of animal species give them an unparalleled vantage point from which to construct an evolutionary pathway of bile acid structure from ancient species to man.

It seems fitting that we begin this series with a review of the newest of insights into bile acid biology and end with a broad view of bile acids encompassing not just decades, but eons. It is a tribute to the many who have pursued this intellectual path that there is such a story to tell. 

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