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EDITORIAL

How we have learned about the complexity of physiology, pathobiology and pharmacology of bile acids and biliary secretion

Jose JG Marin

Jose JG Marin, Laboratory of Experimental Hepatology and Drug Targeting, CIBERehd, University of Salamanca, Salamanca 37007, Spain
Author contributions: Marin JJG is the sole contributor to this paper.
Correspondence to: Jose JG Marin, Professor, Department of Physiology and Pharmacology, Campus Miguel de Unamuno E.I.D. S-09, Salamanca 37007, Spain. jjgmarin@usal.es
Telephone: +34-923-294674 Fax: +34-923-294669
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Abstract

During the last decades the concept of bile secretion as merely a way to add detergent components to the intestinal mixture to facilitate fat digestion/absorption and to eliminate side products of heme metabolism has evolved considerably. In the series of mini-reviews that the *World Journal of Gastroenterology* is to publish in its section of "Highlight Topics", we will intend to give a brief but updated overview of our knowledge in this field. This introductory letter is intended to thank all scientists who have contributed to the development of this area of knowledge in gastroenterology.

Key words: Bile flow; Cholestasis; Hepatocyte; Liver; Transport

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INTRODUCTION

During the last decades the concept of bile secretion as merely a way to add detergent components to the intestinal mixture to facilitate fat digestion/absorption and to eliminate side products of heme metabolism has evolved considerably. In the series of mini-reviews that the *World Journal of Gastroenterology* is to publish in its section of "Highlight Topics", we intend to give a brief but updated overview of our knowledge in this field. The first opening title by Esteller[1], in addition to review the mechanisms of bile formation, will serve as an introduction to the rest of mini-reviews. Therefore, I will skip this task here and devote this letter to thank all scientists who have contributed to the development of this area of knowledge in gastroenterology. First of all, I wish to apology because only a limited number of them will be cited here and also for the fact that, in most cases, I will cite them by the main investigator of the group. I assume that we all know, in some cases personally, what excellent scientists have participated in the contributions published by these teams. Nevertheless, I hope that every important contribution and research group will be cited in the appropriate mini-review of the series. Let me start this brief historical overview by reminding you the important initial steps in understanding bile acid physiology given by Schiff[2] and Wheeler[3], which permitted the establishment of the bases for further investigations by Boyer[4], Erlinger[5], Anwer[6] and others on the role of osmotic mechanisms accounting for bile acid-dependent and-independent fractions of bile flow. The elucidation of the physical-chemical characteristics of bile acids has been determinant in understanding the role of different bile acid species in bile formation, bile acid-induced injury of liver tissue and cholestasis or, in contrast, hepatoprotection, as well as the process of gallstone formation or prevention, *etc.* This has been possible thank to the investigations carried out by many groups, including those of Hofmann[7], Carey[8], Small[7,8], Paumgartner[9], Reichen[9], Danielsson[10], Sjovall[10], Reyes[11], Setchell[12], Poupon[13] and others. It has been with the help of molecular biology techniques that Meier[14,15], Stieger[14], Hagenbuch[15,16], Keppler[17], Thompson[18] and others have been able to identify transport proteins involved in the efficient uptake and secretion of bile acids by the liver. Similar studies by Dawson[16] and others have also contributed to our understanding of the role of intestinal transporters in the so-called enterohepatic circulation of bile acids. Advances in the research of substrate-transporter interactions by many important groups, including several mentioned above in addition to those of Sugiyama[19], Klaassen[20] and Petzinger[21], has lead to Kramer[22] and others, including

our own laboratory[23,24] to undertake the development of promising new drugs based on the substrate selectivity of plasma membrane transporters and the possibility of either blocking their function or targeting bile acid derivatives toward healthy liver tissue or toward tumours located in the enterohepatic circuit. Over the last few years the novel concept of bile acids as signalling molecules in several cell types has emerged. Thus, the possibility that bile acids, as well as other oxysterols, may activate nuclear receptors and regulate the expression of enzymes and transporters was suggested from results obtained at the same time by three different groups[25-27], and developed by these groups, and others, such as those of Karpen[28], Kullak-Ublick[29], Chiang[30] and Houten[31]. These findings are helping us to understand how liver cells may respond to endocrine signals (e.g. during pregnancy) or to the accumulation of bile acids occurring in cholestasis, which is the subject of research currently carried out by several groups, including those of Trauner[32,33], Suchy[33,34], Ananthanarayanan[33,34], Lammert[35], Williamson[35], Accatino[33], Arrese[33,36] and others. Moreover, bile acids can also interact with plasma membrane elements and therefore participate in autocrine and paracrine functions, interacting with several signalling pathways as it is being brilliantly investigated by Haussinger, Kubitz, Keitel and the rest of this group[37], as well as by Dent[38], Fujino[39], Beuers[40], Dufour[41] and others. A complete view of biliary physiology also needs to consider the participation of cholangiocytes in bile formation and the knowledge of mechanisms of bile secretion of other important endogenous compounds, such as cholesterol, bilirubin, glutathione and xenobiotics, such as drugs and toxins. We owe many important contributions in these fields to LaRusso[42], Ballatori[43], Arias[44], Keppler[17], Sugiyama[19], Wolkoff[45], Oude Elferink[46], Meijer[46], Kuipers[46], Jansen[46], Groen[46], Groothuis[46], Ostrow[47], Fevery[48], Coleman[49], Berenson[50], Vore[51] and many others. As I said this editorial letter of gratitude is highly incomplete, but it would be even more so without mentioning the appreciation of many hepatologists to the supporting role of Dr. Falk and the Falk Foundation e.V. to the research in this field.

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