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BILIARY EXCRETION OF DRUGS AND OTHER XENOBIOTICS

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Walter G. Levine
Department of Pharmacology, Albert Einstein College of Medicine, Yeshiva University, Bronx, New York 10461

A thorough understanding of the mechanisms governing the biliary excretion of drugs and other foreign chemicals (xenobiotics) requires an elucidation of the process of bile formation itself. Attainment of such a goal is far from complete, but attention is drawn to recent reviews in this area which may prepare the reader for explorations into xenobiotic excretion (1–4). Briefly, bile production is initiated at the canalicular membranes. With their microvilli, these are well suited for the transport of substances from the hepatocyte into the canalicular lumen. Unlike urine formation, the driving force in bile formation is not hydrostatic pressure since bile flow is seen even in cases where biliary pressure exceeds vascular perfusion pressure. There is good reason to believe that a primary event in bile production is the active transport of bile salts across the membrane, which produces an osmotically controlled secretion of water and accompanying electrolytes. This is termed *bile acid–dependent flow.* From experiments relating bile flow to bile acid concentration, it becomes apparent that there is a substantial bile acid–independent flow as well. This phenomenon is not well understood. Suggestions that the active transport of sodium ion may be involved are based on original observations using inhibitors of sodium transport in the rabbit. Such findings are not readily extrapolated to other species, and the mechanism remains controversial. The possibility of a link between the bile acid–dependent and –independent flows has not been eliminated. There is evidence that secretin-sensitive addition of bicarbonate occurs downstream in the ductules, accounting for the alkaline pH of the bile. Considerable species variations in these mechanisms are seen. Bile salt–independent flow is low in dog and man but may represent a high proportion of total production in the rat. Flow in the rat also appears to be less sensitive to stimulation by secretin than it is in the dog. Studies in humans confirm some of the mechanisms postulated for lower animals. Obviously, much work has yet to be done in this area.

In recent years bile has been recognized as a major route of excretion for many compounds (5–8) and the list of such substances continues to grow in length and

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in diversity. Xenobiotics found in significant amounts in the bile include nearly every class of drugs, numerous physiological compounds, and a variety of toxic and other environmental chemicals. A representative group of such compounds is found in Table 1. Space limitations permit only a partial listing, and in the case of multiple publications on the same compound, the most recent are cited where appropriate.

FACTORS DETERMINING BILIARY EXCRETION

Bile Versus Urine As a Route of Excretion

The mechanism by which the body directs some compounds to the bile and others to the urine is as yet unclear. It is apparent that molecular weight is an important factor. A minimum molecular weight of approximately 325 is required for significant excretion in the rat, while 400 and 475 are the approximate figures in the guinea pig and rabbit, respectively (see 6). The molecular weight threshold is probably 500–600 for humans, although in the absence of extensive studies, it is difficult to make such a generalization. Dyes such as sulfobromophthalein, indocyanine green, and various iodinated cholecystographic media and their respective metabolites, which are known to be excreted in human bile, have molecular weights greater than 600. For the most part these thresholds were originally established using organic anions. More recent work indicates that the threshold for organic cations in the rat may be as low as 200 (66) and shows no species variation. Compounds with molecular weights less than threshold are excreted principally in the urine. However, in the rat, renal ligation does little to increase their biliary excretion. Similarly, compounds with a molecular weight greater than 465 are excreted preferentially in the bile of rats, and after bile duct ligation the urinary excretion of such compounds does not compensate for loss of the major excretory route (67). In the middle lie a number of drugs in the molecular weight range of 355–465 that are extensively excreted in both the urine and bile. For these compounds occlusion of one route of excretion results in a compensatory excretion via the other (67). The molecular size selectivity for urinary and biliary excretion appears to be inherent in the excretory organ itself. Yet there still remains unexplained the group of compounds that appear to have equal affinity for both routes. Some evidence points to reabsorption of foreign compounds as well as normal constituents of the bile within the ductule system. This would contribute to the mechanism of organ specificity observed. However, proof of such a phenomenon awaits more thorough investigation.

Polarity

Drugs excreted in the bile usually require a strongly polar group. This cannot be a sole requirement, however, since even highly charged substances of less than threshold size are not found in the bile. Distinct pathways for organic anions and organic cations have been proposed in addition to a third pathway by which polar but uncharged molecules are excreted. The latter accounts for the excretion of substances such as cardiac glycosides and steroid hormones. These original classifications seem not to be as clear today. For example, bile acids, themselves anions, may not be transported by the usual anionic pathway since they are excreted

normally in Corriedale sheep, which are unable to excrete sulfobromophthalein, an organic acid (68). Bis- and monoquarternary amines may be handled by different pathways (68a). This is inferred from a report that the biliary excretion of *d*-tubocurarine, a bis-quaternary amine, is inhibited by K-strophanthoside while the excretion of procainamide ethobromide, a monoquaternary amine, is unaffected (28). Inhibition of ouabain excretion by dehydrocholate suggests a common pathway, possibly related to the steroid structure found in both compounds (69). Suppression of ouabain excretion by administration of sulfobromophthalein and taurocholate has been reported (70). Thus the apparent pathway for noncharged substances is affected by the presence of organic anions. Furthermore, in rats, administration of the hypolipidemic agent, nafenopin, a tricyclic propionic acid derivative, markedly inhibits the biliary excretion of one organic anion, phenolphthalein glucuronide, but not another, chlorothiazide (71). It would appear that the complexity of these pathways is somewhat greater than originally envisioned and that they may not be entirely independent of each other.

Metabolism

A role for metabolism in biliary excretion is inferred from the observations that most foreign compounds appear in the bile entirely or partially as metabolites. Two aspects of this role are apparent. First, nearly all metabolites, particularly conjugates, are somewhat more polar than are their parent compounds. Second, the molecular weight of the metabolite is usually greater than that of the parent compound. For example, the formation of a glucuronide increases the molecular weight by nearly 200. Thus a compound such as biphenyl would not be expected to be excreted in rat bile because of its low molecular weight of 154 and its nonpolar nature. However, the product of hydroxylation and glucuronidation has a molecular weight of 346, is highly polar, and is readily excreted in the bile (72). Similarly, the carcinogen, 3,4-benzpyrene, is nonpolar and has a molecular weight of 252. However, it is readily excreted in the bile as a complex mixture of hydroxylated and conjugated metabolites (46, 73, 74). In contrast are the dyes phenolphthalein and sulfobromophthalein, which have molecular weights of 318 and 838, respectively, and are each highly polar. Thus they appear to have the prerequisites for significant biliary excretion in the rat. Yet phenolphthalein is excreted in the bile mainly as its glucuronide (72) and sulfobromophthalein as its gluthathione conjugate (75). The di-brom analogue of sulfobromophthalein, phenol-3,6-dibromphthalein disulfonate, is rapidly excreted in the bile metabolically unchanged (76). Thus it is difficult to distinguish those circumstances in which metabolism is a prerequisite for biliary excretion from those in which direct excretion is possible. Apparently the question of structural requirements is not fully answered. The properties of polarity and molecular weight, although they account for many observations, do not entirely explain the relative affinities of many compounds for the biliary tract. So too, the purpose of metabolism is not entirely clear since there appears not to be an absolute requirement for biotransformation for some compounds. Conversely, other compounds that seemingly possess the structural requirements for biliary excretion are metabolized prior to excretion.

Table 1 Drugs and other foreign chemicals excreted in the bile

Compound	Species	Reference
Dyes		
Fluorescein and other xanthine dyes	rat	9
Iodipamide	dog, rat	10
Iothalamate	dog	11
Phenol red	man	12
Sulfobromophthalein	shark, skate	13
Drugs acting in the central nervous system		
Desmethylimipramine	rat	14
Diazepam	man	15
Diazepam	rat	16
Diphenylhydantoin	rat	17
Imipramine	rat	14
Meperidine	man	18
Methadone	rat	19
Morphine	rat	20
Nortriptyline	man	21
Pentazocine	rat	22
Tetrahydrocannabinol	rat	23
Drugs acting on the peripheral nervous system		
Atropine	rat	24
Edrophonium	rat	25
Pentaerythritol trinitrate	rat	26
Terbutaline	rat	27
d-Tubocurarine	rat	28
Antibiotic and other antibacterial agents		
Ampicillin	man	29
Azidocillin	rat	30
Benzylpenicillin	rat	30
Cephaloridine	man	29
Chloroguanide	rat	31
Clindamycin	man	32
Cloxacillin	rat	30
Dapsone	rat	33
Dicloxacillin	rat	30
Erythromycin	man	29
Methicillin	rat	30
Nitrofurantoin	dog	34
Novobiocin	man	29
Oxacillin	rat	30
Quinine	rat	31
Rifamide	man	29
Rifamycin	man	29
Sulfamethoxazole	man	35
Tetracycline	man	29
Thiamphenicol	rat, rabbit, guinea pig, human	36

Table 1 *(Continued)*

Compound	Species	Reference
Diuretics		
Bumetanide	dog	37
Triamterene	rat	38
Drugs affecting the cardiovascular system		
Dicumarol®	rat	43
Digitoxin	rat	39
Digitoxin	guinea pig	40
Digitoxin	human	41
Digoxin	guinea pig	40
Digoxin	man	42
Ouabain	guinea pig	40
Procaine amide	rat	31
Procaine amide ethobromide	rat	28
Carcinogens and other environmental contaminants		
2-Acetylaminofluorene	rat	45
Aflatoxin	chicken	44
3,4-Benzpyrene	rat	46
Butylated hydroxytoluene (BHT)	rat	47
Carbaryl	fish	48
N,N-Dimethylaminoazobenzene	rat	49
7,12-Dimethylbenzanthracene	rat	50
3-Methylcholanthrene	rat	51
Pentachlorbiphenyl	rat	52
Toxic metals		
Arsenic	rat, rabbit, dog	53
Cadmium	rat	54
Lead	dog, rat, rabbit	55
Mercury	rat	56
Steroid hormones		
Estriol	rat	57
Mestranol	rat	58
Norethynodrel	rat	58
Norethynodrel	rat	58
Pregnanalone	rat	59
Testosterone	rat	60
Miscellaneous compounds		
Dipyridamole	rat	31
Indomethacin	rat, rabbit, dog, monkey, guinea pig	61
Methotrexate	rat	62
Methotrexate	man	63
Papaverine	rat	64
Probenacid	rat	65

Phenobarbital is frequently used for investigating the role of metabolism in biliary excretion since it induces the mixed function oxidase which catalyzes the metabolism of most foreign compounds (77). Chronic treatment with this drug enhances the plasma disappearance and biliary excretion of xenobiotics and their metabolites (19, 46, 49, 50, 51, 74, 78–86). However, in addition to inducing the mixed function oxidase, phenobarbital also increases liver size and bile flow (80, 86–90). Two studies can be cited as examples of phenobarbital stimulating biliary excretion by different mechanisms. Goldstein & Taurog (80) reported increased excretion of thyroxin metabolites commensurate with increased bile flow. On the other hand, Levine (46) showed the biliary excretion of metabolites of 3,4-benzpyrene to be markedly increased whether calculated as a function of body weight, liver weight, or bile volume. Here metabolism was the principal factor involved. A dual mechanism for phenobarbital is also apparent in the case of sulfobromophthalein where induced animals not only synthesize the glutathione conjugate more rapidly, but also transport it into the bile more efficiently (86). On the other hand, phenobarbital actually lowers the biliary excretion of morphine (as the glucuronide) although the in vitro metabolism of this narcotic is induced (19). Chronic treatment with phenobarbital also increases the liver content of ligandin (91), a cytosol protein that binds bilirubin and a large number of dyes, drugs, and toxic agents and their respective metabolites (92). Ligandin, after induction, may represent as high as 10% of the cytoplasmic protein, and has been implicated in the uptake of these substances from plasma to liver. Uptake may strongly influence the subsequent fate of these compounds, i.e. biliary transport. Phenobarbital increases hepatic blood flow (93) and in the case of those drugs for which hepatic extraction is high, liver uptake may be flow dependent. Since numerous steps are involved in the hepatobiliary fate of xenobiotics, i.e. uptake, binding, metabolism (for some compounds), intracellular translocation, canalicular transport, it is difficult, if not impossible, to attribute to metabolism alone the action of phenobarbital in biliary excretion. Furthermore, phenobarbital enhances the biliary excretion of a number of chemicals that are not metabolized, e.g. phenol-3,6-dibromphthalein disulfonate (83) and chlorothiazide (81). A further complicating factor is the choleretic effect accompanying the biliary excretion of organic anions such as sulfobromophthalein (94). Thus it is difficult to determine whether the increased dye excretion in phenobarbital-treated rats is caused by the greater bile flow or whether increased bile production is attributable to the osmotic effect of the excreted dye. Roerig et al (95) were able to distinguish between phenobarbital-inducible and -noninducible pathways of methadone metabolism and showed that enhanced metabolism readily explained the greater biliary excretion of methadone metabolites in treated animals. On the other hand, Mulder (96) studied the fate of phenolphthalein, 4-methylumbelliferone, and 8-hydroxyquinoline, each of which is excreted in the bile as its glucuronide, and concluded that the rate-limiting step was not metabolism but canalicular transport of the metabolites.

The properties of increasing bile flow and liver size are not shared by all inducers of mixed function oxidase. Therefore, an alternative means of assessing the role of metabolism in the biliary excretion process involves the use of 3,4-benzpyrene and 3-methylcholanthrene as inducing agents. Pretreatment with these compounds in-

duces the metabolism of a narrower spectrum of drugs than does phenobarbital and does not appreciably increase liver size or bile flow 24–48 hr after a single injection (97), a time when metabolism is known to be greatly induced. Thus, with no change in liver weight or bile flow, 3,4-benzpyrene enhances thyroxin excretion as its glucuronide (80). After injection of the carcinogens, 3,4-benzpyrene, 3-methylcholanthrene, 7,12-dimethylbenzanthracene, 2-acetylaminofluorene, or N,N-dimethylaminoazobenzene, biliary excretion of their metabolites is increased in rats pretreated with either 3,4-benzpyrene or 3-methylcholanthrene (45, 46, 49–51). Conversely, inhibitors of the mixed function oxidase, for example, SKF 525A, piperonyl butoxide, metyrapone, and emetine, suppress the biliary excretion of these metabolites. The inducers and inhibitors affect the in vitro metabolism of the carcinogens in a manner parallel to their effects on excretion in vivo. Furthermore, if the metabolic steps are bypassed by injecting mixtures of the metabolites rather than the parent compound, the biliary excretion rate is much greater and is unaffected by inducers or inhibitors. It was concluded that these agents act primarily on metabolic and not transport steps and that metabolism is the rate-limiting process in the overall hepatobiliary fate of these carcinogens. For other compounds as well, metabolism may be rate limiting in biliary excretion. This was implied for diphenylhydantoin based on more rapid excretion after injection of its major metabolite (17). Biliary excretion of digitoxin and its metabolites is increased by pretreatment of rats with two inducing agents, pregnenoline-16-α-carbonitrile and spironolactone, to an extent that far exceeds the accompanying increase in liver size and bile flow (39, 98). The proportion of polar metabolites, which are mainly glucuronides, increases after treatment with these agents (39). Two other inducers, phenobarbital and 3-methylcholanthrene, are without effect. Although these observations strongly imply that metabolism controls the biliary excretion rate of digitoxin, in vitro metabolism must be carried out to support such a conclusion. In particular the lack of effect of phenobarbital and 3-methylcholanthrene may shed considerable light on mechanisms of digitoxin metabolism if studied in vitro. Excretion of ouabain, which is not metabolized in the rat, increases slightly after pregnenolone-16-α-carbonitrile and spironolactone, implying a nonmetabolic effect on excretion. However, such an effect would appear to contribute little to the enhanced excretion of digitoxin metabolites.

Effects of Other Xenobiotics

Many drugs and chemicals induce cholestasis and thus block biliary excretion (98a). α-Naphthylisothiocyanate, which produces cholestasis, probably acts by way of a toxic metabolite found in the bile. Inhibitors of protein synthesis, for example, cycloheximide, actinomycin D, and ethionine, block both the biliary excretion of the toxin as well as its cholestatic effect (99), suggesting that protein synthesis is required for synthesis of the metabolite. Some xenobiotics depress the biliary excretion of others without causing cholestasis. Competition for transport may explain some of the latter findings. In other cases the mechanisms are obscure. Treatment of rodents with the hypolipedimic drug, nafenopin, increases the size of the liver, promotes a considerable choleresis, and inhibits the biliary excretion of a number

of substances (71, 100–104). Compounds affected include organic anions (104) and noncharged compounds (101), but not organic cations (100). Transport of these substances from plasma to liver and liver to bile is significantly suppressed while their metabolism is little affected. It follows then that nafenopin does not affect the biliary excretion of 3,4-benzpyrene, which appears in the bile as a mixture of polar metabolites, since metabolism is the rate-limiting step in the excretion of this carcinogen (46). However, excretion of injected metabolites is depressed since there is no further metabolism and only transport is involved (103). Administration of the insecticide, mirex, also elicits a hepatomegalic and choleretic effect. There is a marked impairment of biliary excretion of polychlorinated biphenyls, imipramine, and sulfobromophthalein
appreciably affected (105, 106). This is accompanied by an efflux of the nonexcreted metabolites into the perfusing medium. The antibiotic, novobiocin, which interferes with the glucuronidation of bilirubin, blocks the biliary excretion of 3-trifluoromethyl-4-nitrophenol (107) and warfarin (108). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, although a potent inducer of the mixed function oxidase, suppresses biliary excretion of indocyanine green, a nonmetabolized dye (109).

A xenobiotic may appear to inhibit its own excretion. During infusion of sulfobromophthalein at rates equalling or surpassing maximum hepatic transport capacity, there is a diminished bile flow and a decrease in the excretion of the dye and its gluthathione conjugate (110, 111). A partial explanation may be that sulfobromophthalein inhibits the canalicular transport of its glutathione conjugate since the decrease in bile flow and excretion is not seen during infusion of the conjugate (111,112). Sulfobromophthalein also inhibits mitochondrial respiration (113) which may relate to the effect on dye transport and bile flow. In view of these observations, considerable doubt is cast on the use of the Bromsulphalein test to assess hepatic transport capacity (T_m).

Sex

A number of sex differences in biliary excretion have been noted that do not necessarily relate to the well-documented sex differences in drug metabolism seen in the rat (114). Tartrazine is excreted metabolically unchanged more efficiently in female rats than in males (115), although the difference disappears during the early stages of liver regeneration (116). Aldosterone metabolites are excreted more rapidly in females than in males (117). Therefore, the mechanism of the sex difference must be inherent in the hepatic transport systems. Indocyanine green, which is not metabolized, is excreted more rapidly in female rats than in males (81), and phenobarbital stimulates excretion only in males. Chlorothiazide, another nonmetabolized drug, is excreted more efficiently in males than in females and phenobarbital stimulates excretion in females but depresses it in males (81).

Species

All species studied can excrete foreign compounds and their metabolites in the bile, although most studies have been carried out in rats. Not the least of the advantages of the rat is the absence of a gall bladder, which simplifies the problem of direct collection of hepatic bile. Differences in molecular weight thresholds, as discussed

above, account for much of the reported species variation. On the other hand, ouabain, which has a molecular weight of 574 and appears in the bile metabolically unchanged, is excreted rapidly in the rat and slowly in the dog and rabbit (118). The excretion of disodium chromoglycate is high in the squirrel monkey (78–82%) and low in the rabbit (3–15%) (119). Other species show intermediate values. Although molecular weight thresholds vary considerably with species, this is not evident for organic cations (66). Nevertheless, dogs excrete the quaternary amine, procainamide ethobromide, very poorly compared to rats and rabbits (120).

Route of Administration

The route of administration of drugs may also influence excretion pathways. Direct administration into the portal circulation might be expected to result in more extensive biliary excretion compared to the systemic route. Indeed, portal vein infusion of valethamate bromide, scopolamine-N-butyl bromide, and QX-572, a lidocaine-like antiarrhythmic compound, results in far greater biliary excretion of the compounds than is seen during fermoral vein infusion (121).

ENTEROHEPATIC CIRCULATION

The products of biliary excretion are deposited in the duodenum and may subsequently be excreted in the feces or reabsorbed and reenter the blood. The cycle of enterohepatic circulation is responsible for the conservation of a large number of substances within the body. The best known of these are the bile salts, more than 90% of which are retained after biliary excretion. For many drugs enterohepatic circulation influences their duration of action. Frequently, prior to biliary excretion a compound is converted to its glucuronide in the liver which ordinarily would be too polar for significant absorption. However, the bacterial flora within the large bowel contain a glucuronidase capable of hydrolyzing the conjugate and releasing the free drug which can then be reabsorbed. The formation and subsequent hydrolysis of other conjugates may also occur. Support for the role of intestinal bacteria is found in experiments in which antibiotics are administered to suppress these organisms resulting in the inhibition of the enterohepatic circulation (20, 122, 123). Among the numerous compounds for which enterohepatic circulation has been demonstrated are estrogenic and progestational steroids (58, 124, 125), digitoxin (41), pentaerythritol trinitrate (26), morphine (20), bis(*p*-chlorophenyl) acetic acid (126), mercurials (56), arsenicals (53), and indomethacin (61). Diazepam has been reported to undergo enterohepatic circulation in man (15) but not in rat (16). This is an example of species specificity not readily explained by different molecular weight thresholds. The enterohepatic circulation of indomethacin varies greatly in rats, dogs, and monkeys (127), which readily explains the species differences in the fate of this drug. The enterohepatic circulation is dealt with more extensively in a recent review (128). Some work in this area involves simply following blood levels of a drug with and without biliary drainage. Until each step in the phenomenon is properly investigated, any conclusion concerning the enterohepatic circulation of a drug must be treated with considerable caution.

TOXICITY ASSOCIATED WITH BILIARY EXCRETION

It has been suggested that bile acids such as lithocholic acid and deoxycholic acid may act as promoters of colon carcinogenesis, as seen experimentally in rats using azoxymethane, dimethylhydrazine (129), and 3'-methyl-4-dimethylaminoazobenzene (130). Intestinal lesions associated with indomethacin are probably related to biliary excretion of the drug (61). A possible role of bile salts in this effect is implied from the lowering of the incidence of this lesion by administration of cholestyramine, which combines with bile salts in the intestines preventing their reabsorption. However, it is difficult to distinguish between a causal and permissive role of bile salts in this instance.

SUMMARY

A vast number and variety of xenobiotics appear in the bile. For some this is a final excretory process, for others it is merely one step in the active enterohepatic circulation. For still others it may be a vital step in a toxicologic or carcinogenic process. During the past ten years there has been a steady accumulation of observations in the literature bearing on biliary excretion mechanisms. Phenomena such as molecular weight thresholds and other aspects of species variation as well as response to inducing agents are described in many papers and much speculation is available as to their meaning. The clinical significance of this work is still somewhat dependent upon results obtained from lower animals, although studies occasionally appear on patients who have temporary bile drainage subsequent to surgery. It is important that efforts persist in obtaining data in humans since extrapolation from lower animals in the area of drug dispostion is often precarious. The basic physiological and biochemical mechanisms governing the biliary fate of drugs and other xenobiotics have yet to be elucidated fully. Perhaps the use of drugs and other pharmacological tools will hasten progress toward this goal.

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