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Enterohepatic circulation of organochlorine compounds: a site for nutritional intervention☆

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Abstract

Organochlorine compounds enter the body primarily as components of the diet. Their removal from the body is via excretion into the feces. There is evidence that many people are in a positive balance, with the rate of intake of organochlorines exceeding that of their excretion. A desirable nutritional approach to this problem would both reduce dietary intake and increase fecal excretion. Nonabsorbable dietary lipids reduce the absorption of dietary organochlorines and also increase the rate of their fecal excretion. Organochlorine compounds that are stored in the body enter the intestine both in bile and through a poorly understood nonbiliary mechanism. Part of the amount that enters the intestine is excreted, and part is reabsorbed in an enterohepatic circulation. There is evidence that an increase in excretion can be achieved by interference with the enterohepatic circulation of organochlorine compounds and their metabolites. Data from animals and humans show that the presence of nonabsorbed lipid in the intestine can increase the rate of excretion in a clinically significant manner.

Keywords: Organochlorine; Intestine; Absorption; Enterohepatic; Orlistat; Olestra

1. Introduction and background

The treaty known as the Stockholm Convention on Persistent Organic Pollutants restricts the production and use of 12 persistent organic pollutants (POPs). These compounds, which include polychlorinated biphenyls (PCBs), dioxins and dichlorodiphenyltrichloroethane (DDT) are all organochlorine compounds. As of August 2005, 105 countries (not the United States) had ratified the treaty.

The chlorine-carbon bonds common to these POPs contribute to two important physicochemical properties — stability and lipophilicity. This chemical stability has resulted in the persistence of POPs in the ecosphere and in biological tissues. The lipophilicity directs POPs to stored triacylglyerol both in plants and in animals.

Although the effort to reduce the production of POPs is an important step toward amelioration of their toxic effects, the environmental and biological half-lives of these compounds ensures that they will remain an ecological problem for many decades. In addition, the production of flame retardants and other halogenated organic compounds is introducing new stable, lipophilic compounds into the food chain.

Given the inability to remove toxic lipophiles from the environment within the foreseeable future, we need to consider alternative approaches to deal with their threat to human health. We review here the results of studies that focus on intervention that can lessen both the availability and body burden of organochlorine compounds (OCs) in humans.

2. Organochlorines in human tissue

There is ample evidence that OCs are present in humans. Studies of breast milk composition have revealed the international presence of OCs [1]. A memorable demonstration of the ubiquitous distribution of OCs in humans resulted from a meeting of 13 European Health ministers in June 2004. All of the ministers volunteered to have OCs measured in their blood, and most of the assayed OCs were found in all of the ministers.

There are also reports that the level of OCs in blood increases with age [2,3]. This longitudinal increase results only if the rate of intake is greater than the rate of excretion.

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Since the presence of OCs in the human food chain will continue for decades, it is unlikely that cessation of production of OCs will contribute significantly to health in the foreseeable future. We therefore need to consider alternative approaches to potential health problems resulting from OCs. One approach is that of reducing the human body burden of OCs by nutritional means. We present here data that suggest that it is possible to reduce the rate of intake of dietary OCs and to increase the rate of excretion of OCs.

3. Organochlorine lipophilicity

As noted above, OCs are lipophilic. The lipophilicity of a compound can be quantified by the oil/water partition coefficient, the ratio of concentration of the compound in octanol to that in water. This coefficient, expressed as its logarithm (base 10), is given for a number of compounds in Table 1.

The affinity for a lipid phase results in a high level of storage of OCs in adipose tissue in animals [6]. In addition, this lipophilicity provides a nutritional approach to reduce the body's rate of intake and to increase the body's rate of excretion of OCs. We focus on this approach in the succeeding presentation of data and discussion.

4. Fat Absorption

Essentially, all of the dietary fat that humans ingest is in the form of triacylglycerol, glycerol linked by ester groups to three fatty acids. In most countries, most of these fatty acids have chain lengths of 16 or 18 carbon atoms. The digestion and absorption of dietary fat requires the hydrolysis of the fat to form 2-monoacylglycerol and two fatty acids. These hydrolysis products form mixed micelles with bile acids and are absorbed into the enterocyte where they are synthesized into new triacylglycerol molecules. These triacylgycerols are transported in lymph with lipoproteins in chylomicron particles. Mattson et al. [7–9] demonstrated that alcohols with ester links to six or eight fatty acids are not hydrolyzed by pancreatic lipase in the small intestine, and importantly, they are not absorbed from the intestine into the lymph.

Lipophilic dietary constituents such as cholesterol and fat-soluble vitamins enter the small intestine with dietary fat. They partition into the mixed micelles described above and are absorbed from the micelles into the enterocytes.

In the normal fat absorption process, the presence of an oil phase in the small intestine is transient, since rapid hydrolysis and absorption results in disappearance of essentially all triacylglycerol before it passes from the proximal to the distal small intestine. Fats that are not hydrolyzed and absorbed maintain an oil phase during gastrointestinal transit through all of the small and large intestines.

Table 1
Partition coefficients of lipophilic and hydrophilic compounds

Compound	Log (octanol/water)
β-Carotene	17.6[a]
Cholesterol	8.7[a]
DDT	6.9[a]
Hexachlorobenzene	5.7[b]
Aspirin	1.1[a]
Glucose	−2.4[a]

[a] Ref. [4].
[b] Ref. [5].

5. Enterohepatic circulation

Compounds may enter the intestine from sources other than the diet. Bile acids, phospholipids and cholesterol, for example, enter the intestine as components of bile. They are, to varying extents, absorbed again from the intestine and then return to the liver and bile where the cycle of biliary excretion and reabsorption recur. This process is known as enterohepatic circulation. Enterohepatic circulation conserves bile acids as they undergo excretion and reabsorption 4 to 15 times per day in normal humans [10].

6. Organochlorine compound entry into the intestine

As noted above, OCs enter the human intestine in the diet. Interference with the absorption of dietary OCs by nutritional intervention is a strategy to reduce systemic accumulation of OCs.

OCs also enter the intestine carried in bile and by a poorly understood nonbiliary mechanism. This nonbiliary mechanism has been observed for OCs, such as chlordecone. Fecal excretion of chlordecone was found to be the same in rats with or without biliary diversion [11]. Presumably OCs enter the intestine by secretion out of the enterocyte, or by turnover of enterocytes that contain significant amounts of OCs.

Organochlorine compounds and their metabolites also undergo enterohepatic circulation. Early evidence of this phenomenon occurring in humans was reported by Cohn et al. [12]. Subjects who had been exposed to chlordecone were treated with the unabsorbed resin cholestyramine. The half life of chlordecone in the blood decreased by 50% with the cholestyramine treatment. This result was interpreted as interruption of the reabsorption of chlordecone that entered the intestine by binding to the lipophilic backbone of the cholestyramine. The increase in the rate of reduction of the body burden reflected a reduced efficiency of enterohepatic circulation.

7. Nonabsorbable lipids and dietary OCs

As we further discuss below, nonabsorbable lipids and OCs interact in a manner that can decrease the body burden of OCs. The properties of nonabsorbable lipids (lipophilicity, resistance to pancreatic lipase) and the properties of OCs

(lipophilicity of parent compound and metabolites) set the stage for their interaction in the body.

The most direct interaction between OCs and nonabsorbable lipids occurs when OCs are in the diet. As noted above, the presence of OCs in foods is essentially inescapable. Simultaneous ingestion of OCs and nonabsorbable lipids can result in dissolution of OCs in the nonabsorbable oil phase in the mouth and stomach and/or partition of the OCs into the nonabsorbable oil phase in the small intestine. Although a portion of OCs can partition into the intestinal mixed (bile salt, polar lipid) micellar phase, a significant amount will be carried into the colon and stool by the oil phase.

Early studies demonstrated this effect for the lipophile, cholesterol and DDT. In the rat, Mattson et al. [13] reported a linear decrease in cholesterol absorption when the nonabsorbable lipid, olestra, replaced soybean oil in the diet. When olestra accounted for 50% of the dietary fat, cholesterol absorption was approximately one third of that seen without dietary olestra. In humans, inclusion of 14 g/d of olestra in the diet decreased cholesterol absorption from 56% to 47% of that ingested [14].

The observations of the effects of olestra on dietary cholesterol were extended to the OC-DDT. Volpenhein et al. [15] reported that replacement of half of dietary soybean oil with olestra reduced the lymphatic appearance of dietary DDT to one third of that seen with soybean oil without olestra. DDT in feces increased, and DDT in the carcass decreased with substitution of olestra for soybean oil.

8. Nonabsorbable lipids and enterohepatic OCs

It was observed that the inclusion of olestra in the diet increased the rate of excretion of cholesterol that was not of dietary origin [16]. Rats were intravenously injected with ^{14}C–DDT, and the fecal excretion of ^{14}C in the neutral sterols significantly increased. This result was consistent with interference with the reabsorption of cholesterol that entered the intestine in bile, reflecting dissolution in the nonabsorbable oil phase.

It was also found that a nonabsorbable fat increased the rate of excretion of ^{14}C in gerbils that were given dietary ^{14}C–cholesterol and allowed to attain a steady fractional excretion rate [17]. The rate of excretion was doubled when olestra was included as 10% of the diet and was approximately eightfold higher when the regimen included both dietary olestra and reduced caloric intake. The data are consistent with reduced reabsorption of enterohepatic circulating DDT (and its metabolite, DDE [1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene]) by the presence of a nonabsorbable lipid in the intestine.

The use of the nonabsorbable lipid, olestra, in the treatment of a patient who had been highly exposed to PCBs was reported by Redgrave et al. [18]. The adipose tissue level of PCBs decreased dramatically during a 2-year regimen of approximately 20 g/d of olestra.

9. In vivo generation of a nonabsorbable oil phase

Tetrahydrolipstatin (orlistat) is a potent inhibitor of pancreatic lipase that acts through covalent bonding of the lipase molecule [19]. Inhibition of pancreatic lipase has the result of maintaining an oil phase in the intestine consisting of unhydrolyzed dietary fat. This fat moves from the small intestine to the large intestine and the feces.

We proposed that the unabsorbed intestinal fat resulting from orlistat ingestion can reduce the enterohepatic circulation of an organochlorine, hexachlorobenzene (HCB). Hexachlorobenzene that has been absorbed from the diet is known to enter the intestine both in bile and through a poorly understood nonbiliary route [20]. We measured the effect of orlistat on the excretion of HCB in mice that had been given ^{14}C–HCB by oral gavage.

Mice were gavaged with ^{14}C–HCB, and feces were collected. Two groups of animals were fed diets with 25 or 50 ppm orlistat prior to the gavage. Fecal excretion was measured for all animals, and absorption of HCB was the same with or without orlistat. This result undoubtedly reflects the fasting state of the animals during gavage. For the duration of the study after the gavage, six mice received the control diet without orlistat, 12 received a diet with 25 ppm orlistat and 12, a diet with 50 ppm orlistat. On days 10 and 11 after the gavage, feces were collected, and excreted HCB was measured. The results are shown in Fig. 1. Total fat excreted by the 25 ppm orlistat group was measured to be 5% of dietary fat, and that excreted by the 50 ppm group, 10%. These excretion values are based on total fat balance analysis, which has errors (food spillage, coprophagy, missing fecal pellets) that cause a bias toward calculations that are lower than the actual percent excretion. These values do, however, support the conclusion that the level of orlistat in the diet resulted in an amount of fecal fat which is attained in typical use of orlistat [21].

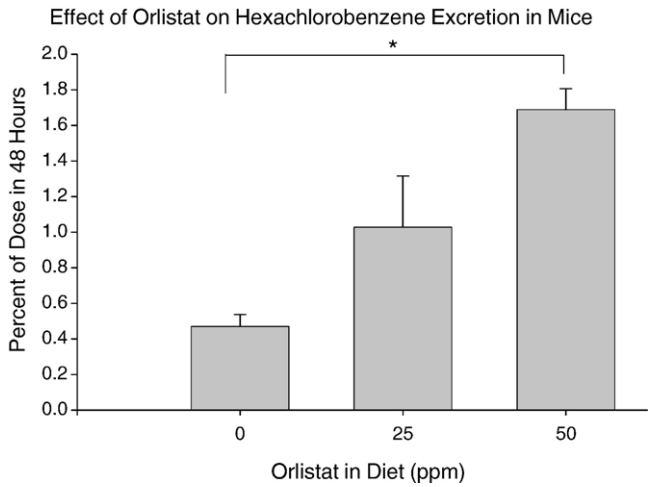

Fig. 1. Hexachlorobenzene in feces as a function of dietary orlistat (mean and S.E.M.; $n=6$ for 0 ppm orlistat; $n=12$ for 25 and 50 ppm orlistat). *50 ppm is different from control, $P<.005$).

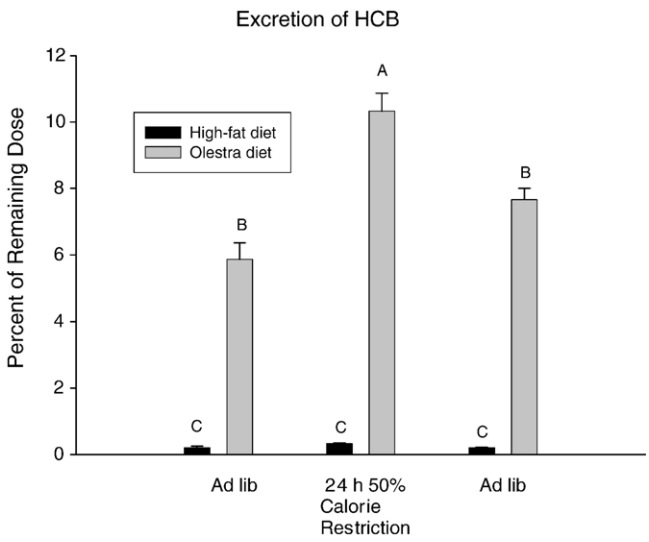

Fig. 2. Hexachlorobenzene in feces. Mice were gavaged with ^{14}C–HCB and then received either a high-fat diet or diet with added olestra. Diets were ad lib. or calorically restricted by 50%. Values with different letters are significantly different ($P<.001$; $n=8$ per group; mean and S.E.M.; analysis of variance).

10. Changes in body weight and enterohepatic circulation

Numerous studies have found that OCs and their lipophilic metabolites are stored in adipose tissue [6,22]. In addition, it has been reported that reduction in caloric intake mobilizes the stored OCs from adipose tissue and results in distribution into other tissues and organs [23,24].

There is evidence that this redistribution involves movement of OCs from adipose to the blood circulation with an increase in the biliary and nonbiliary transport of OCs into the intestine. Mutter et al. [17] reported an eightfold increase in the fecal excretion of DDT and DDE in the gerbil when caloric restriction was combined with nonabsorbable lipid in the diet relative to the excretion with the nonabsorbable lipid alone.

A regimen of caloric restriction and nonabsorbable lipid decreased movement of HCB from adipose tissue to brain relative to that seen with caloric restriction alone [6]. The amount and concentration of HCB in the brain was reduced by one third by dietary nonabsorbable lipid.

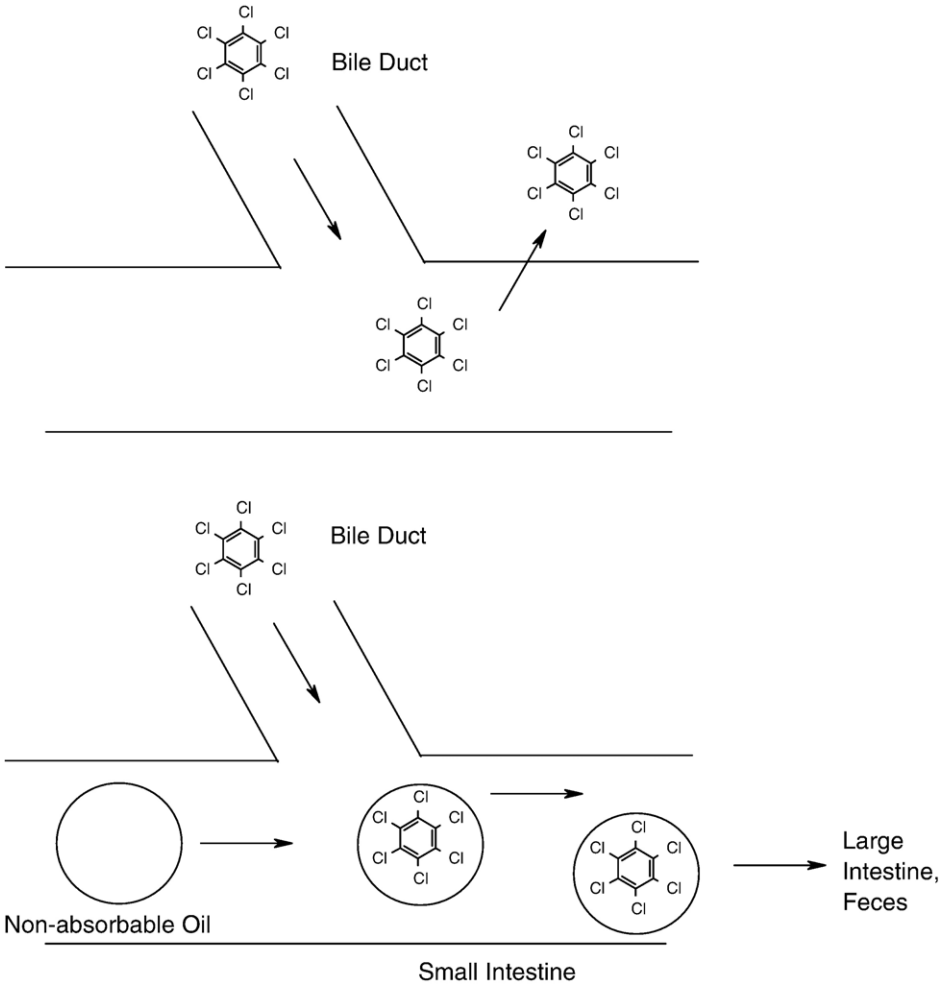

Fig. 3. The top panel describes the enterohepatic circulation of hexachlorobenzene that enters the intestine in bile. The bottom panel illustrates the effect of a nonabsorbable oil on the reabsorption of hexachlorobenzene.

We sought to determine whether or not short-term negative caloric balance would enhance the enterohepatic circulation of OCs, with the rationale that generation of a short-term lipolytic state would mobilize the OC from the adipocyte. We measured fecal excretion of HCB from mice that had been orally gavaged with ^{14}C-HCB during short periods of ad lib. feeding and of caloric restriction. The mice received either a high-fat diet (control) or a diet that included 10% by weight of the nonabsorbable fat, olestra. Olestra markedly increased the excretion of HCB relative to the control in all dietary regimens. Olestra plus caloric restriction increased excretion more than olestra without caloric restriction (Fig. 2).

11. Conclusion

The small intestine is a site that provides an opportunity for nutritional intervention that can decrease intake and increase excretion of ubiquitous and persistent OCs. Nonabsorbable fat in the diet or generated in the intestine can interfere with the absorption of OCs that enter the intestine in the diet or as part of enterohepatic circulation. The effect on enterohepatic circulation is described in Fig. 3.

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