REVIEW ARTICLE

Present understanding of the interaction of drugs and food during absorption

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In spite of increasing evidence that the action of drugs may enhance or impair the intestinal absorption of nutrients and vice versa, the mechanisms underlying these interactions remain to be clarified. To provide better understanding of the problem, this communication includes a brief survey of major factors involved in absorption of both drugs and nutrients. Typical examples of the interaction of drugs and foodstuffs on the absorption of one or the other are reviewed with reference to the mechanism of action whenever possible.

Absorption of drugs

This is governed by lipid solubility, by rate of dissociation (characterized by pK_a) and pH of medium, by particle size and by physical form (Table I). With few known exceptions drugs cross the gastric and/or intestinal mucosa by passive non-ionic diffusion. Weak acids ($pK_a > 2$) are absorbed in the stomach, weak bases ($pK_a < 8$) in the upper intestine. Neutral substances display no definite preference for the site of absorption. Digestive enzymes are not involved and competitive inhibition (decreased absorption of a substance caused by preferential absorption of another substance, both using common metabolic pathways) does not appear to occur. These rules however, probably cannot be fully applied to actively transported drugs such as pyrimidines or cardiac glycosides.[15, 23]

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Absorption of food

Conversely, this depends mainly on the presence of gastrointestinal secretions, on pH and on enzymatic activity of absorptive cells. With the exception of vitamin B_{12} the major bulk of nutrients is absorbed in the upper intestine. Several mechanisms are involved, including passive diffusion, active transport and specialized routes of absorption. The degree of lipid solubility is important only for lipids; water-soluble nutrients are absorbed and transported by the non-lipid phase of intestinal contents. Some nutrients (e.g. simple sugars or amino acids) display competitive inhibition.[5]

A. Effect of drugs upon absorption of nutrients

Many different drugs may cause gastrointestinal symptoms such as nausea, vomiting and diarrhea. Certain drugs have been shown at times to affect the absorption of food. The responsible mechanisms may be related to either the intraluminal or the absorptive phase of metabolism. The following groups of drugs are of special interest in regard to food absorption:

(1) Drugs affecting gastric and/or intestinal motility.
(2) Hypocholesterolemic drugs.
(3) Surfactants.
(4) Antimicrobial agents.
(5) Cytotoxic drugs.
(6) Anticonvulsants.

(1) *Drugs affecting gastrointestinal motility.* Cathartics form a mixed group having diverse chemical structure and mechanism of action.[15, 68] Several cathartics have been shown to decrease absorption of nutrients. Oxyphenisatin, bisacodyl and phenolphthalein may inhibit intestinal uptake of glucose in man and rat, whereas anthraquinone derivatives have no such effect.[19] Vitamins A, D, E and K are soluble in liquid paraffin, and because the latter is itself poorly absorbed, a deficiency of liposoluble vitamins may result. Faulty absorption of vitamin D then interferes with calcium absorption.[68] Hypertonic solutions of mannitol are capable of injuring the absorptive cells, leading to inhibition of transport of glucose, water and sodium across intestinal mucosa.[44]

Certain ganglion-blocking drugs such as methantheline bromide (Banthine) or hexadecyltrimethylammonium (Centrimonium) are said to inhibit absorption of some nutrients by their action on the autonomic system of the gastrointestinal tract.[14, 45]

(2) *Hypocholesterolemic drugs.* It has been shown that cholestyramine, a basic ionic polystyrene (molecular weight about 1,000,000) forms unabsorbable complexes with bile acids, preventing recirculation of the latter to the liver.[61] This in turn increases breakdown of cholesterol to bile acids and eventually results in a lowering of serum cholesterol levels. This effect of

cholestyramine on bile acids has been utilized in the treatment of pruritus of obstructive jaundice[9, 61] and of hypercholesterolemia.[1] Removal and fecal loss of bile acids by cholestyramine precipitation may induce steatorrhea in man[61, 72] and the rat,[18] although the absorption of medium-chain triglycerides does not appear to be affected. Curiously, in the malabsorption associated with a high intestinal concentration of bile acids, as occurs following resection or bypass of ileum, cholestyramine treatment may prove beneficial.[55]

Triparanol (MEH 29), another hypocholesterolemic drug, has been shown to induce structural changes and decreased mitotic activity in the intestinal mucosal cells, which may result in steatorrhea, azotorrhea and other symptoms of malabsorption.[41] The effect of a third drug of this group, neomycin sulfate, is rather complex and will be considered subsequently.

(3) *Surfactants.* Several years ago it was demonstrated that Tween 80 (polyoxyethylene (20) sorbitan mono-oleate), a non-ionic surfactant, improved the absorption of vitamin A in malabsorption syndrome.[25] In an earlier study[29] carried out in a patient with blind-loop syndrome due to adhesions, we have shown that the addition of Tween 80 enhanced the absorption of neutral fat and vitamin A, but did not affect the absorption of glycine. The duodenal juice of this patient apparently lacked the ability to form a stable emulsion. This was probably due to bacterial deconjugation of bile acids. The addition of Tween 80 allowed a fine emulsification of fat. Also we have demonstrated[31, 33] that administration of Tween 80 together with cream resulted in a significant increase of alimentary lipemia in patients following cholecystectomy. It has been shown[33] that Tween 80 will enhance absorption of ingested cholesterol in the rat.

The favourable effect of Tween 80 on fat emulsification might imply a similar beneficial influence on pancreatic lipase; however, this is not the case. It has been shown that Tween 80 inhibits lipolytic activity present in the pancreatic juice of man and rat.[33, 43] Fortunately, bile acids prevent this adverse effect of Tween 80.[43] We observed[33] that Tween 80 added to normal human duodenal juice failed to inhibit lipolysis *in vitro*.

Finally, it should be emphasized that surfactants in general may affect absorption not only by way of fat dispersion but also by direct effect on the permeability of the lipoprotein membrane of mucosal cells. Also it must be mentioned that opinion on the effect of Tween 80 on fat absorption is not unanimous.[33]

(4) *Antimicrobial drugs.* Both *in vitro* and *in vivo* it has been shown that some antibiotics may activate or inhibit enzymatic systems participating in the digestion and absorption of food. The effect produced depends upon the particular system and the dose of antibiotic used. Thus, it has been demonstrated that a low concentration of chlortetracycline (CTC) stimulates the activity of pancreatic amylase, cellulase and protease in piglets, whereas higher levels inhibit proteolytic systems.[64]

Other studies[52-54] have suggested that *in vitro* CTC inhibits the activity of pancreatic lipase and alpha-amylase of the rat, mouse and dog. The inhibition requires the presence of calcium or other bivalent cations in the system. Subsequently we demonstrated[30, 32, 33] that CTC inhibits human pancreatic lipase to a significant degree and prevents formation of a stable emulsion *in vitro* in concentrations corresponding to a dilution of the "optimal dose" (250 mg.) in 10 ml., 100 ml. or even 1000 ml. of intestinal contents.

In further research we have confirmed[35, 36] the adverse effect of CTC on intraluminal lipolysis both in intact rats and in rats with isolated (ligated) duodenal loops. Simultaneously, a certain decrease of fat absorption has been observed. On the other hand, in patients without evidence of organic gastrointestinal disease the effect of CTC administration on intraluminal hydrolysis of olive oil was far less pronounced and often unpredictable.[32, 33] It has to be ad-

TABLE I
Some characteristics of absorption of drugs and food

Factor	*Effect upon:* *Absorption of drugs*	*Absorption of food*
Lipid solubility	When increased, absorption of most drugs is enhanced	Important for pathway of transport
pH	Affects pK_a, solubility and stability of drugs; dependence on pH absorption may be increased or diminished	Similar effects on proteins, lipids and electolytes; also affects activity of digestive enzymes
Dissociation (pK_a)	When increased, absorption of most drugs reduced	Not well known
Particle or Molecular size	When increased, absorption reduced	Upper limit of size, above which absorption is negligible
Passage through "water pores" occurs	From molecular weight < 100	From molecular radius 4 - 5 Å
Route of absorption	Mainly non-ionic diffusion; active transport in few drugs	Non-ionic diffusion; active transport; specific routes
Site of absorption	Stomach or intestine	Major part in upper intestine, except vitamin B_{12}
Participation of specific factors		
— digestive enzymes	None	In proteins, lipids and carbohydrates
— other factors	Not observed	In some, e.g. iron, calcium, lipids, vitamin B_{12}
— competitive inhibition	Not observed	Described in simple sugars and amino acids
— saturation phenomenon	Not observed	Described

mitted that an unequivocal interpretation of our results was not possible, as no reliable indicator of intestinal fat metabolism was available.*

The studies of lipolysis in man referred to indicated that therapeutic doses of CTC do not affect adversely the absorption of fat. Indeed, the administration of CTC prior to or simultaneously with a fatty meal (cream) did not influence the course of alimentary lipemia in healthy volunteers, nor was steatorrhea induced in patients who received standard treatment with CTC for respiratory infection.[32, 33]

The discrepancy between the results obtained in man and in the rat could be due to several factors, including difference in species, dosage of CTC and varying experimental conditions. Our further *in vitro* studies disclosed[32] another important factor relating to the presence and concentration of bile acids in the medium. In the presence of bile acids the inhibitory effect of CTC is suppressed; this protective effect increases as the concentration of bile acids rises. It is noteworthy that the rat has no gallbladder and that the concentration of bile acids in the upper intestine is lower than in man.[33] It would be of interest to examine the effect of CTC on fat absorption in patients with impairment of biliary and/or pancreatic secretion. Our preliminary (unpublished) studies have been so far inconclusive.

In 1959 we demonstrated[30, 33, 34] that other antibiotics of this group such as tetracycline and oxytetracycline are also capable of inhibiting lipolysis and impairing the stability of emulsions *in vitro*. Furthermore, tetracycline may cause a decrease of absorption of amino acids, fat, iron or xylose by a direct injurious effect on the intestinal mucosa of the rat.[17, 71] Curiously, administration of CTC to chicks results in thinning of the intestinal wall and reduction in intestinal weight.[37] The mechanism of this strange effect and its importance for food absorption have not yet been elucidated.

The basic antibiotics also are of considerable interest, particularly in relation to neomycin sulfate. We noted[30, 34] that neomycin sulfate, streptomycin and bacitracin have a deleterious effect on digestion of fat in the presence of human duodenal juice similar to that of CTC. These observations were later confirmed by others.[42] Subsequently it has been shown[11, 13] that the addition of neomycin to bile or to micellar solutions causes precipitation of bile acids. The overall effect of neomycin on lipolysis cannot, however, be explained by its influence on bile acids alone, since inhibition appears to occur even in their absence.

In a series of studies we have shown[35] that neomycin sulfate significantly inhibits lipolysis and absorption of olive oil from isolated duodenal loops of rats. Administration of this antibiotic to intact rats, however, did not affect seriously the digestion of fat, but resulted in reduction in alimentary lipemia.[36] The unfavourable influence of neomycin on intraluminal lipolysis has been confirmed in man.[52]

As occurs with cholestyramine, bile acids precipitated by neomycin cannot be recirculated to the liver and are eventually excreted in the stool.[11] The removal of bile acids from enterohepatic circulation has two important consequences: (a) increased catabolism of cholesterol in the liver and decline of its level in the blood[48, 58] and (b) steatorrhea.[52] Administration of ox bile has been reported to improve this malabsorption.

Neomycin may also impair absorption by a direct effect on the intestinal mucosa of man, causing reversible changes in the villi, namely increased cellularity of lamina propria and the occurrence of pigment-containing macrophages in the mucosa.[10, 24] This toxic effect appears to be exerted chiefly on crypt cells. The activity of several mucosal enzymes has been found to be decreased. It is interesting that in the rat the injurious influence of neomycin on intestinal mucosa is far less pronounced or even absent.[6, 10]

The adverse effects of neomycin on fat digestion and on the intestinal mucosa are believed to be responsible for the steatorrhea and azotorrhea which may occur in healthy subjects.[12, 24, 48, 52] An accumulation of fat in the jejunal mucosa has been reported, and also malabsorption of carotene, hexoses, iron and vitamin B_{12}.[10, 12, 24]

There is evidence too that polymyxin and bacitracin may cause slight malabsorption of fat, carbohydrates and proteins and also a decline in serum cholesterol; simultaneously, the fecal output of bile acids increases.[48] Similarly, kanamycin has been shown to increase fecal fat and nitrogen in man.[13] In general, the effect on absorption of these antibiotics is less striking than that of neomycin.

Another interesting action of antibiotics is the inhibition of protein synthesis in absorptive cells. Puromycin administration to rats blocks protein synthesis necessary for chylomicron formation and causes accumulation of fat in the intestinal mucosa.[57] Actinomycin is capable of inhibiting the formation of vitamin-D-induced protein in the intestinal mucosa of the rat and consequently blocks the active transport of calcium across the intestinal wall.[46] Cycloheximide inhibits synthesis of ribosomal protein and thereby inhibits the uptake of iron or leucine by the intestinal mucosa of the rat.[17]

It should be remembered that antibiotic therapy may induce a serious intestinal dysmicrobia which, itself, may cause secondary malabsorption.

The influence of sulfonamides on food absorption has had insufficient investigation. According to an early study,[47] administration of sulfonamides caused a delay in gastric evacuation of food. Recently it has been reported that para-aminosalicylic acid therapy is associated with impaired absorption of vitamin B_{12}.[21]

(5) *Cytotoxic drugs.* Colchicine, administered parenterally to rats, induces changes in the intestinal mucosa, including villous atrophy, cellular invasion of the lamina propria and arrest of mitosis.[4, 16] Simultaneously, an inhibition of mucosal enzymatic activity and a block of water, electrolyte and xylose transport occurs. In man, a single dose induces non-specific changes in the intestinal mucosa, a decrease of disaccharidase activity and a decline in absorption

*Polyethylene glycol (PEG) or phenol red, used as a marker, separates in the stomach and intestine from the lipid phase of food.[67] Also, we have demonstrated[63] that PEG can partially inhibit pancreatic lipase and impair emulsification of fat *in vitro*.

of fat, carotene and vitamin B_{12}, accompanied by increased fecal excretion of nitrogen and electrolytes.[49, 66] A reduction in serum cholesterol levels may also be present. Fortunately, these changes are reversible. The decrease of vitamin B_{12} absorption may help to explain the occasional occurrence of megaloblastic anemia during colchicine treatment.

In the rat, aminopterin inhibits mitosis and induces atrophy and other reversible changes of the intestinal mucosa.[50, 69] Injections of this drug cause block of mucosal disaccharidase activity and impairment of fat absorption.[50] In dogs, low absorption of xylose has been reported.[69]

Methotrexate in rats causes injury of the intestinal absorption surface confined mainly to the crypt cells.[38] After treatment is discontinued, the rate of mitosis in crypt cells is increased above normal. In man, parenteral administration of methotrexate is followed by nonspecific changes in the jejunal mucosa.[62] The influence of this drug on absorption is not yet known.

(6) *Anticonvulsant drugs.* Clinical observations suggest that some agents of this group may interfere with folic acid absorption. Phenobarbitone and phenytoin impair xylose absorption in man. Addition of folic acid corrected this defect.[51] Diphenylhydantoin and related drugs may cause a significant but reversible decline of serum folate levels in both children and adults.[8]

Many other drugs occasionally can affect the absorption of nutrients. In this regard the deleterious effect of tranquillizers such as trifluoperazine (Stelazine) on absorption of vitamin B_{12} and xylose is pertinent.[51] Chlorpromazine and diphenhydramine hydrochloride (Benadryl) have been shown to inhibit the transport of amino acids across the intestinal mucosa of rats.[3] Another unusual observation is malabsorption of fat and nitrogen induced by administration of phenindione.[26]

Other agents such as hormones, diuretics, ethanol etc. may affect absorption and bidirectional transport of nutrients in the gastrointestinal tract. Detailed discussion of these effects is beyond the scope of this paper.

B. Effect of food upon absorption of drugs

Knowledge of this reverse process is relatively limited. First of all, the usual method of investigation, by estimation of blood levels of the absorbed drug, is an unsatisfactory means of assessing intestinal absorption. The actual level of the drug depends not only on its absorption but also on its removal from the blood stream. Furthermore, some drugs are degraded or inactivated during gastrointestinal passage, and the chemical method may estimate only the unchanged part of the absorbed drug.[60] In antibiotic studies the antimicrobial activity of serum can be used as an indicator of absorption. However, the actual concentration of the drug may be different from these levels.[22]

Most studies are concerned with the effect of food on the absorption of antibiotics. Prior ingestion of food (one-half to one hour before) causes a decline in blood levels of orally administered crystalline penicillin K, benzylpenicillin G, oxacillin and 2-biphenylpenicillin.[20, 28, 56] Oddly, the closely related drugs, phenoxymethylpenicillin (V) and alpha-aminobenzylpenicillin, are not affected by food.[20, 27] One interesting study has shown that the composition of a meal may affect the absorption of an antibiotic. Simultaneous ingestion of whole milk, buttermilk or cottage cheese induced a significant decrease in blood levels of orally administered demethylchlortetracycline (Declomycin).[59] If no milk product was included, the meal had no effect on serum antibiotic concentration. The authors suggest that this effect of milk might be due to chelation of demethylchlortetracycline by calcium caseinate complex, rendering it no longer available for absorption.

It appears that the effect of food on antibiotic absorption also depends on the lipid solubility of the drug. Prior ingestion of a fatty meal resulted in a significant increase of serum levels of water-insoluble griseofulvin.[7] This effect increased as the dietary fat load was raised. If no fat was included in the meal, no rise in blood levels of griseofulvin was observed. Experiments carried out with erythromycin suggest that the effect of food on absorption of the antibiotic may also depend on gastric acidity.[22] Prior ingestion of breakfast affected adversely blood concentrations of erythromycin base, propionate or stearate, whereas in achlorhydria due to pernicious anemia no such unfavourable effect of food has been recorded. In general, the levels of erythromycin stearate were lower than those of other derivatives. An adverse effect of food on absorption of lincomycin[2] but not of clinimycin has been observed.[65]

Only a few careful studies concerning other drugs have been reported. Prior ingestion of food causes decreased blood levels of orally administered derivatives of acetylsalicylic acid in man.[70] An early paper claimed that the effect of food on absorption of sulfonamides depended largely on their chemical structure.[47] Recent studies have shown no significant differences in absorption between sulfadimethoxine, sulfamethoxypyridazine and sulfisoxazole.[39] Simultaneous ingestion of food regularly caused reduced absorption of these drugs.

The *mechanisms* of these varied effects of food on absorption of drugs are poorly understood, but obviously they are not uniform. Presence of food in the gastrointestinal tract induces changes in pH, osmolality, motility and secretion. These effects are largely dependent on the composition of the meal.[5, 14] In turn they may affect ionization, stability, solubility, intestinal transit and absorption of drugs. Several other possible mechanisms by which food may influence drug absorption include the formation of insoluble complexes (e.g. with starch) or the dilution of a drug in a component of identical polarity.[40, 68]

More questions are probably raised than answered by this review. This whole topic is of great physiological and therapeutic interest, and it is surprising that many unresolved problems have received so little attention. Without doubt the eventual application of isotopic and balance techniques and other modern investigational methods will clarify much that remains unanswered.

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Note: References listed under the numbers 29-36 and 63 refer to experiments performed in the Institute of Human Nutrition in Prague, Czechoslovakia.