drugs also need to be resistant to degradation/metabolism during this passage. All drugs that are absorbed from the stomach, small intestine and upper colon pass into the hepatic portal system and are presented to the liver before reaching the systemic circulation. Therefore, if the drug is going to be available to the systemic circulation, it must also be resistant to metabolism by the liver. Hence, an oral dose of drug could be completely absorbed but incompletely available to the systemic circulation because of *first-pass* or *presystemic* metabolism by the gut wall and/or liver.

Gut wall metabolism

The gut walls contain a number of metabolizing enzymes that can degrade drugs before they reach the systemic circulation. For example, the major cytochrome P450 enzyme CYP3A, present in the liver and responsible for the hepatic metabolism of many drugs, is present in the intestinal mucosa and intestinal metabolism may be important for substrates of this enzyme. This effect can also be known as *first-pass metabolism by the intestine*. CYP levels tend to be higher in the intestine than in the colon.

Hepatic metabolism

The liver is the primary site of drug metabolism and thus acts as a final barrier for oral absorption. The first pass of absorbed drug through the liver may result in extensive metabolism of the drug, and a significant portion may never reach the systemic circulation, resulting in a low bioavailability of those drugs which are rapidly metabolized by the liver. The bioavailability of a susceptible drug may be reduced to such an extent as to render the gastrointestinal route of administration ineffective, or to necessitate an oral dose which is many times larger than the intravenous dose, e.g. propranolol. Although propranolol is well absorbed, only about 30% of an oral dose is available to the systemic circulation owing to the first-pass effect. The bioavailability of sustained-release propranolol is even less as the drug is presented via the hepatic portal vein more slowly than from an immediate-release dosage form, and the liver is therefore capable of extracting and metabolizing a larger portion. Other drugs which are susceptible to a large first-pass effect are the cholesterol lowering agent, atorvastatin, the anaesthetic lidocaine (lignocaine), the tricyclic antidepressant imipramines and diazepam and the analgesics pentazocine and morphine.

First-pass metabolism can be avoided by drug administration to the mouth (buccal or sublingual; see Chapter 30) or to the rectum (see Chapter 42). The arrangement of the blood vessels in these regions means that absorbed drug does not pass through the liver first, prior to entering the systemic circulation.

Summary

There are many physiological factors that influence the rate and extent of drug absorption; these are initially dependent on the route of administration. For the oral route, the physiological and environmental factors of the gastrointestinal tract, the gastrointestinal membrane and presystemic metabolism can all influence drug bioavailability.

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