Section Five: Sites of Drug Metabolism

Chapter 35

Introduction: Pathways of Drug Metabolism

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When drugs enter the body, the majority of them are metabolized and transformed partly or wholly into other substances. These transformations are catalysed by enzymes which are found mainly in the liver, although they are also found in lesser amounts in other tissues such as intestine, kidney and lung. Although the majority of drugs are metabolized in the body there are some which are not metabolized at all and are excreted unchanged, whereas there are others which change spontaneously into other substances without the participation of enzymes. From the point of view of their fate in the body drugs can therefore be divided broadly into three types as follows:

a) drugs which undergo enzyme catalysed transformations
b) drugs which are not metabolized and are excreted unchanged
c) drugs which undergo spontaneous reactions when given the appropriate physical conditions such as pH or when they contact a suitable physiological compound with which they can react.

The majority of drugs belong to type a, but some drugs can undergo a combination of enzyme catalysed and spontaneous reactions. Although enzyme catalysed reactions are carried out by the tissues of the body, it is now becoming clear that some transformations of drugs can also be carried out by the gut flora (Scheline, 1968).

A. The Biphasic Metabolism of Drugs

The reactions which drugs undergo can be classified as oxidations, reductions, hydrolyses and syntheses. Because of the nature of these reactions and the biological activity of the products, it is convenient to regard the metabolism of drugs as occurring generally in two phases (Williams, 1959). The oxidations, reductions and hydrolyses occur in the first phase and can result in

1. the inactivation of a drug
2. the conversion of an initially inactive compound into an active drug
3. the conversion of an active drug into another active drug.

The second phase of drug metabolism consists of synthetic reactions, most of which convert active compounds into inactive excretory products. This concept of drug metabolism can be represented as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase I</th>
<th>Oxidation reduction and/or hydrolysis products</th>
<th>Phase II</th>
<th>synthetic or conjugation products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>activation or inactivation</td>
<td>Phase I</td>
<td>inactivation</td>
<td>products</td>
</tr>
</tbody>
</table>

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Phase I reactions usually introduce into the drug molecule groups such as OH, COOH and NH₂ which enable the phase I products to undergo the synthetic reactions frequently referred to as conjugations. If the drug already contains any of the above groups, e.g. phenol, then it can undergo conjugation directly without the intervention of a phase I reaction. Sometimes, a drug may undergo only phase I reactions as in the case of ethanol, which is oxidized mainly to CO₂.

In both phases the polarity of the drug is usually increased; the products of phase II are strong organic acids and, occasionally, strong organic bases, which are readily excreted. To illustrate let us consider the metabolism of the well-known antipyretic and analgesic drug, phenacetin (Smith and Williams, 1949). This drug is a neutral lipid-soluble compound which is oxidatively de-ethylated in the first phase of its metabolism to the weak acid, p-acetamidophenol, which has a pKa of about 10. In the second phase, p-acetamidophenol is conjugated mainly with glucuronic acid to give p-acetamidophenylglucuronide which is a strong acid with a pKa of about 3.5. At the pH of the blood this glucuronide is virtually completely ionized, highly water-soluble and readily excreted by the kidney.

\[
\text{CH}_3\text{CONH} \quad \text{Phase I} \quad \text{CH}_3\text{CONH} \quad \text{Phase II} \quad \text{CH}_3\text{CONH} \\
\text{OC}_2\text{H}_5 \quad \text{p-acetamidophenol} \quad \text{p-acetamidophenylglucuronide} \\
\text{Phenacetin} \quad \text{pKa ca. 10} \quad \text{pKa ca. 3.5} \\
\text{neutral} \quad \text{ca. 0.25\%} \quad 99.99\% \\
\text{(ionization} \quad \text{at pH 7.4)}
\]

It appears, therefore, that drugs are metabolized in the body along pathways which tend to lead to the formation of water-soluble, polar compounds which are readily excreted. Both phenacetin and its phase I metabolite, p-acetamidophenol, are active drugs but the activity of phenacetin is largely due to this metabolite. The phase II metabolite, p-acetamidophenylglucuronide, is an inactive excretory product and its formation terminates the activity of phenacetin.

**B. Phase I Reactions**

The reactions of drugs which can be classified as oxidations, reductions and hydrolyses are carried out by enzymes which occur predominantly in the liver, although some metabolizing activity is also to be found in extrahepatic tissues such as the kidney and intestinal tissue and to a lesser extent in the lungs, adrenals and blood. The majority of these reactions are carried out by enzymes located in the endoplasmic reticulum of the hepatic cells (Brodie et al., 1955; Gillette, 1963). On homogenization of the liver, the endoplasmic reticulum is disrupted, giving rise to small vesicles which can be separated from the homogenate by high-speed centrifugation to give the fraction called microsomes. Many of the reactions of drugs can be carried out *in vitro* with the microsomes and suitable co-factors, particularly reduced nicotinamide-adenine dinucleotide phosphate (NADPH).

The oxidative reactions carried out by the microsomes have been extensively studied (Gillette, 1963, 1966) and it has been shown that the oxidizing system contains at least two catalysts, namely the NADPH-oxidizing flavoprotein, known as NADPH-cytochrome c reductase and a CO-binding haemoprotein called cytochrome P-450 (see chapter 38, this volume). Microsomal oxidation of drugs has a specific requirement for NADPH and molecular oxygen and the system fits into the category of mixed-function oxidases. Detailed accounts of the