CYTOCHROME P450-DEPENDENT MONOOXYGENASE: AN OVERVIEW

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INTRODUCTION

In early studies on liver microsomes it was noticed that the heme content, measured by the pyridine hemochrome method, yielded values about double that of the content of the only known microsomal hemoprotein, cytochrome b5 (1). Reduction of the microsomes with sodium dithionite yielded, in the presence of carbon monoxide a "carbon monoxide-binding pigment" which was rationalized as not to be a hemoprotein (1, 2). The reasons cited for the CO-binding pigment not to be a hemoprotein included a) the absence of a reduced minus oxidized difference spectrum in the Soret region, b) lack of α- and β-peaks for the reduced, CO-complex, c) displacement of the CO-reduced absorption peak much further to the red than other carbon monoxy-hemoproteins, and d) the CO-complex showed no photodissociation. P450 was coined as a tentative name for the CO-complex, which was first reported to be hemoprotein in nature, in 1962 (3). Within the next few years cytochrome P450 was demonstrated to be the terminal oxidase in a number of microsomal monooxygenation reactions (4, 5).

Cytochrome P450 is actually a family of different gene products, all with a single iron protoporphyrin IX prosthetic group containing a fifth ligand to the sulfur atom of a cysteine residue. A large number of cytochrome P450 forms have already been sequenced, all of which contained the cysteinyI group of the carboxy-terminal portion of the molecule in a region of highly conserved amino acids, and enough sequence similarity to crystallized, Pseudomonas P450 (P450CAM), the structure of which is known (6), to allow attempts to relate functional regions, e.g., heme binding, oxygen-binding, and substrate-binding domains (7, 8). Several of the subsequent chapters in this book discuss specific forms of cytochrome P450 and their structure, and the interaction of the cytochrome P450 with other microsomal electron transfer proteins.

Cytochrome P450 Catalyzed Reactions

Cytochrome P450 is a very versatile enzyme. It can catalyze a very wide range of different types of reactions, as pointed out by Gillette and by Brodie many years ago (9). These include a variety of reaction types (Figure 1), from oxidative deamination, desaturation of steroids, various heteroatom dealkylations and oxidations hydroxylations and a
REATIONS CATALYZED BY

CYTOCHOME P450

1. DEAMINATION

\[ \text{amphetamine} \xrightarrow{\text{NADPH}} \text{N-methylamphetamine} \]

2. DESATURATION

\[ \text{testosterone} \xrightarrow{\text{NADPH}} \text{estrone} \]

3. DEALKYLATIONS

A. NITROGEN

\[ \text{aminopyrine} \xrightarrow{\text{HCHO}} \text{N-demethylaminopyrine} \]

B. OXYGEN

\[ \text{p-nitroanisole} \xrightarrow{\text{HCHO}} \text{p-hydroxyanisole} \]

C. SULFUR

\[ \text{6-methylthio purine} \xrightarrow{\text{HCHO}} \text{6-hydroxy-6-methylthiopurine} \]

4. HYDROXYLATIONS

A. ALIPHATIC

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{COOH} \xrightarrow{\text{NADPH}} \text{HOCH}_2\text{CH}_2\text{CH}_2\text{COOH} \]

B. AROMATIC

\[ \text{aniline} \xrightarrow{\text{HCHO}} \text{hydroxyaniline} \]

5. HETEROATOM OXIDATION

A. N-OXIDATION

\[ \text{Sulfanilamide} \xrightarrow{\text{HCHO}} \text{Nحو} \]

B. S-OXIDATION

\[ \text{Chlorpromazine} \xrightarrow{\text{HCHO}} \text{Sульфапирамид} \]

C. O-OXIDATION

\[ \text{testosterone} \xrightarrow{\text{HCHO}} \text{hydroxytestosterone} \]

Figure 1