Role of Phase I Metabolism in Drug Activation and Clinical Treatment Outcomes

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This chapter explores the relation between drug biotransformation and pharmacological activity. More precisely, it surveys the formation of active metabolites and exemplifies cases of metabolites as or more active than the parent drug. Because very few drug conjugates are pharmacologically active, the focus is on metabolic reactions of functionalization (i.e., phase I), namely, oxidations, reductions, or hydrolyses.

The first section sets the scene by explaining the pharmacokinetic/pharmacodynamic (PK/PD) interplay that underlies drug action, and the existing continuum ranging from drugs devoid of active metabolites, to drugs yielding some active metabolite(s), to prodrugs whose activity is due solely to the metabolite. Soft drugs are briefly exemplified since they nicely illustrate the concept of drugs designed to be rapidly metabolized to inactive, atoxic metabolites.

The second section is dedicated to drugs whose activity depends in part on the presence of one or more active metabolite(s). Thus, the drug’s action can be prolonged, as exemplified with diazepam and some other benzodiazepines. Alternatively, a drug’s pharmacological spectrum can be broadened by a metabolite; witness the antinociceptive activity of codeine, which is essentially due to its metabolite morphine. In another scenario, both the drug and its metabolite contribute comparatively to the clinical effect (e.g., tramadol). Finally, a drug such as tamoxifen is metabolized to one or more highly active metabolite(s).

The third section covers carrier-linked prodrugs, the examples presented therein having been selected to illustrate significant objectives in prodrug design. Thus, fospropofol was developed with the aim of overcoming a pharmaceutical hurdle, namely the low solubility of propofol. The lack of oral absorption of the anti-influenza agent Ro-64-0802 was overcome using simple physicochemical principles, namely, by masking its highly hydrophilic carboxylate group with a bioreversible ester function to yield oseltamivir. Another strategy to improve oral absorption is by targeting intestinal transporters, as illustrated with valacyclovir. The last example, capecitabine, exemplifies a more ambitious objective, namely, tissue targeting via organ-selective activation.

The fourth section deals with another class of prodrugs known as bioprecursors. Here, metabolic activation is by redox modification of a functional group, without cleavage of a promoiety. Four examples are presented, namely, nabumetone, a longacting non-steroidal anti-inflammatory (NSAI) prodrug with low gastric toxicity, the two anti-aggregating agents clopidogrel and prasugrel, whose bioactivation unmasks a highly reactive sulfenic acid group, and tirapazamine, an antitumor bioprecursor activated by reduction to a DNA-damaging radical. Clopidogrel is treated in some detail to illustrate the influence of genetic factors on clinical outcomes.

The fifth section briefly illustrates drug–drug interactions (DDIs) at the metabolic level, taking the antiretroviral protease inhibitors (PIs) as a case in point. A concluding section then completes the chapter.

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