Abstract:
Cytochrome P450 is a microsomal membrane-bound protein that metabolizes xenobiotic compounds, mainly: pollutants, environmental compounds, and drugs; and is principally located in the liver. CYP2D6 is one of several P450s that primarily metabolizes 30% of pharmaceuticals such as anti-arrhythmics, anti-depressants and beta blockers. Research on P450s is extremely valuable to the pharmaceutical industry because CYP2D6 binds with, as substrates and inhibitors, drugs such as: codeine, quinidine, fluoxetine, and ritonavir. Regarding metabolism and inhibition, it is possible to predict how drugs will work by how they fit into the CYP2D6-binding site. CYP2D6 has a heme group and five amino acids that particularly impact binding. These five include: glutamate 216 which is part of the F-G helix, aspartate 301 which is along the I-helix, and phenylalanines 102, 481, and 483. The heme group in the binding site is responsible for carrying out the hydroxylation of substrates. Unluckily, if a drug can fit well into the site it may be metabolized before it has worked; if a drug fits, but not close enough to the heme to get hydroxylated, it can result in interactions because it will block the site when another drug molecule needs access. Therefore, the Cytochrome P450 system has a key role in pharmacology.

Drug Design

? Most drug discovery screens include a test for CYP2D6 binding or metabolism
? Medicinal chemists need to understand the CYP2D6 binding site, to design drugs that will not be metabolized too fast
? Diagnosing which mutant form of CYP2D6 a person may have, not everyone does, allows the tailoring of specific drugs and/or doses to a person’s genetic makeup—this is personalized medicine. This prevents a potentially toxic buildup of the drugs in the system. Also, it can predict if higher doses are needed due to faster breakdown by CYP2D6.

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