OPEN ACCESS Freely available online

Enzyme Engineering

ISSN: 2329-6674

Commentary

Drug Metabolism and Elimination Interactions Caused by Enzyme Inhibition

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DESCRIPTION

Enzymes are biological catalysts that act to increase a reaction without being altered or used up. They are unique to a single type of reaction and one or a small number of related reactants called as substrates. Enzymes are an essential part of the cell because many biological reactions would proceed too slowly without them to support life. Enzymes, which are protein catalysts, have no effect on the thermodynamics and they influence the kinetics of a reaction. However, they can increase the rate of a chemical reaction and maintain equilibrium.

A substance that blocks the action of an enzyme is called as enzyme inhibition. Enzymes help speed up chemical reactions in the body and take part in many cell functions, including cell signalling, growth, and division. Enzyme inhibitors may be used in clinical treatment of cancer to prevent the growth of certain enzymes required by cancer cells. Nearly every cell process is catalyzed by enzymes. Modifiers are inorganic and organic molecules that alter the catalytic activity of specific enzymes. Activators (positive modifiers) are molecules that increase enzyme activity, while inhibitors (negative modifiers) are molecules that decrease enzyme activity.

Enzyme inhibitors are substances that slow down the rate of an enzyme-catalyzed reaction by turning the enzymes into inactive substances, this process is called as enzyme inhibition. Two classes of enzyme inhibitors are generally identified, depending on whether the enzyme-inhibitor complex separates rapidly or very slowly, it can be reversible or irreversible.

Enzyme inhibition slows down drug metabolism, which makes a substrate drug more likely to cause side effects and toxicity to increase its systemic exposure. The metabolism is decreased by enzyme inhibition, particularly of the Cytochrome P450 (CYP) enzymes, which in turn increases the action of other drugs that are inactivated by the enzyme. Because several protease inhibitors are potent CYP inhibitors, these effects can be clinically significant and major considerations in the treatment of HIV-infected patients with combination therapy. Several drug metabolism inhibitors selectively affect the metabolism of various stereoisomers, making life even more difficult.

Some drugs therapeutic effects are a direct consequence of the inhibition of particular enzymes. Allopurinol potentiates and prolongs the activity of mercaptopurine (the active metabolite of azathioprine), which is metabolised by xanthine oxidase and is one of several cytotoxic and immunosuppressive medicines. Disulfiram, an aldehyde dehydrogenase inhibitor used to cause an unpleasant reaction to ethanol, also blocks the metabolism of other drugs, including warfarin, which it makes stronger. This enzyme is also inhibited by the antibiotic metronidazole, which is used to treat anaerobic bacterial infections and a number of protozoan diseases. Because of this, patients who are given metronidazole should avoid alcohol. Even though enzyme inhibition is not the primary mechanism of action of the offending agents, there are also examples of drugs that inhibit the metabolism of other drugs. Consequently, glucocorticoids and cimetidine enhance a variety of drugs, including some antidepressants and cytotoxic drugs.

Loss of activity can occur when a prodrug's conversion to its active metabolite is inhibited. Due to the fact that clopidogrel is frequently used in conjunction with other antithrombotic drugs that increase the risk of stomach bleeding, proton pump inhibitors and omeprazole have been frequently prescribed together. Omeprazole inhibits an active metabolite produced by CYP2C19 that is the mechanism by which clopidogrel functions, possibly reducing the antiplatelet effect. The Food Drug Administration (FDA) continues to advice against using these drugs concurrently for this reason, despite the fact that the clinical significance of this is still unknown.

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Received: 28-Feb-2023, Manuscript No. EEG-23-21766; **Editor assigned:** 02-Mar-2023, Pre QC No. EEG-23-21766 (PQ); **Reviewed:** 16-Mar-2023, QC No. EEG-23-21766; **Revised:** 23-Mar-2023, Manuscript No. EEG-23-21766 (R); **Published:** 30-Mar-2023, DOI: 10.35248/2329-6674.23.12.203

Citation: Demir M (2023) Drug Metabolism and Elimination Interactions Caused by Enzyme Inhibition. Enz Eng. 12:203