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Preview

Protecting Against Cocaine, Heroin, and Sarin Gas

The first X-ray structure of human carboxylesterase 1 (hCE1) and the structures of hCE1 with drug analogs bound reveal important molecular details of how the drugs cocaine, heroin, and tacrine are metabolized and cleared.

The human body has a number of enzymatic systems to degrade foreign substances. Until recently, little was known at a molecular level about the how the body recognized and cleared the drugs cocaine and heroin. Two recent papers by the Redinbo group at the University of North Carolina at Chapel Hill [1, 2] have taken important strides toward elucidating the binding mechanism and specificity of the clearance enzyme human carboxylesterase 1 (hCE1). hCE1 helps to eliminate cocaine, heroin, and a number of other drugs (Figure 1). In addition, the enzyme is capable of detoxifying the highly poisonous nerve agents sarin, soman, and tabun, which have been used to kill thousands of human beings in detestable acts of mass genocide.

How and why has the body evolved a mechanism for handling these substances? Why would our bodies have a way of recognizing and clearing cocaine, heroin and artificial substances such as sarin gas? The answer lies in the constant chemical warfare being waged by living organisms against each other. Man did not invent chemical warfare; the masters of that art are the plants. Many plants consume large amounts of metabolic energy to produce toxic compounds to defend themselves with. Plants, after all, cannot run away when attacked, but must respond to whatever threat attacks them while remaining in one place. A particularly dramatic example of this are the cyanogenic compounds found in many acacia trees. When the leaves of these acacias are crushed, a cyanogenic β-glucoside, prunasin, normally isolated in a vacuole, is cleaved by a β-glucosidase, and poisonous cyanide gas is released [3]. The purpose of this reaction is, almost certainly, to discourage animals from eating the plant's leaves. The plant's chemical attack rarely kills the feeding animals, since the animals have evolved their own defensive mechanisms to degrade the plant's compounds in the constantly escalating ecological war for survival. However, the compound will often make the animals ill, thus limiting the number of leaves the animal eats. In highly evolved ecosystems, these animal-plant relationships become balanced, with animals eating enough of the plant to survive but not enough to overwhelm the plant population.

Although it is not known which animal the poppy plant evolved opium to combat, in a bizarre twist of fate the plant has become widely domesticated by man due to opium's addictive properties. Thus, the poppy plant has become widely spread and is nurtured by farmers in many third world counties for the economic benefit of selling the opium-containing flowers—an example of evolution in action.

Although they are illegal, the addictive properties of cocaine and heroin drive numerous people to take large quantities of these drugs in spite of vigorous law enforcement activity and penalties. If the levels of these drugs rise too high in the serum level, they will kill the user by an overdose, making these drugs very dangerous to self-administer. Fortunately, or unfortunately, from the addict's point of view, the substances are cleared from the body by a series of enzymatic steps. hCE1 hydrolyzes the methyl ester linkage of cocaine to generate benzoylecgonine, which is then excreted in the urine (Figure 2). When cocaine is ingested with alcohol, hCE1 can also hydrolyze cocaine to cocethylene, which is more toxic than cocaine itself. hCE1 also hydrolyzes heroin, a commonly abused derivative of opium, to 6-acetyl morphine and to morphine. One of the questions the Redinbo group hoped to answer with their investigations was how these two structurally diverse compounds could be recognized in the body by the same enzyme.

Unlike in anabolic metabolism, where, in general, each enzyme acts upon one specific substrate and produces one product, xenobiotic metabolism utilizes enzymes that can each recognize a wide variety of substances. The quintessential example of this are the cytochrome P450s. One of these, CYP3A4, can metabolize about 60% of the common pharmaceutical small molecules on the market. Often the substances that the enzyme recognizes appear to have little in common structurally. In their elegant work, the Redinbo group has used the structures of hCE1 bound to analogs of cocaine and heroin [1] and to the Alzheimer's drug tacrine [2] to dissect out the common features of the binding site that allow for specific recognition and the parts of the active site that are relatively nonspecific. Particularly interesting are the multiple binding modes observed for the bound tacrine molecules.

Multiple binding modes is an emerging theme in the binding to active sites involved in clearing xenobiotics such as P450s [4] and PXR [5]. The knowledge of how compounds bind to hCE1 will be valuable in the future to researchers designing new drugs, as it can be used to predict, in silico, whether a compound is likely to metabolized by hCE1. If enough structural information of this type is available for xenobiotic enzymes, it will allow the development of a good in silico ADME/tox model of human biochemical systems. This should lead to faster, more successful drug designs, as the clearance rate of drugs can be more accurately tailored without using expensive animal models.

If hCE1 can clear heroin and cocaine, can it be used to treat overdoses of these compounds? The Redinbo group thinks so. hCE1 has a long plasma half-life, 620 hr, and is not immunogenic [1]. Injecting hCE1 into the bloodstream of an overdosed patient should allow the body to clear the drug more quickly and potentially could save the patient's life. hCE1 may also be used to protect

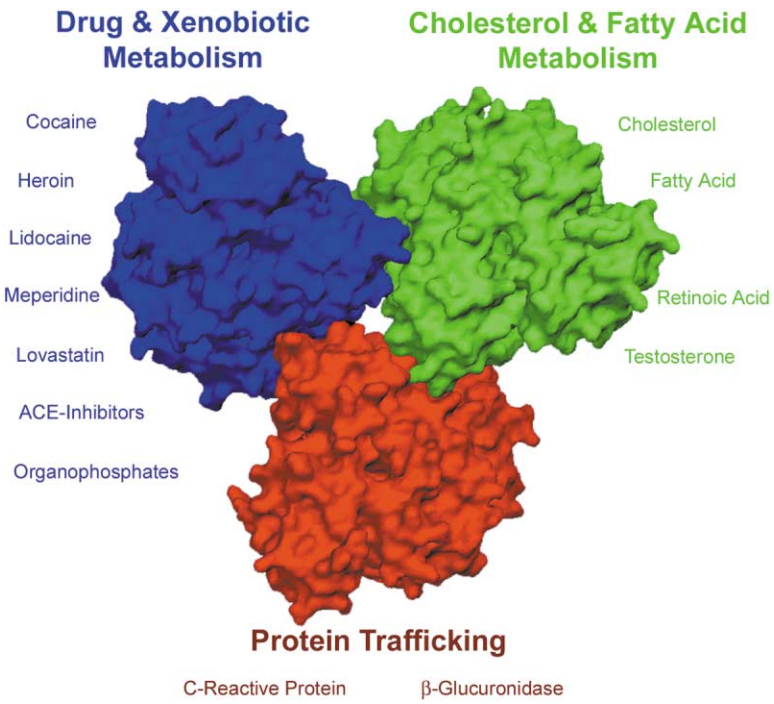

Figure 1. Compounds and Pathways that Involve Human Carboxylesterase 1 Are Arranged around the Trimeric Form of the Enzyme

a soldier from deadly sarin gas on the battlefield. It would act much longer and provide a different kind of protection than the presently used injection of atropine, and could thus be administered prior to an attack.

However, the general-purpose hCE1 has a relatively slow rate of catalysis compared to specialized metabolic enzymes. This means that for hCE1 to be truly useful in treatment of gas poisoning and overdoses, it will need to be engineered into more specific and active forms. Such work is already underway in the US Army [6, 7] and in the Redinbo laboratory, as well as other places.

In short, the elegant work of the Redinbo group offers

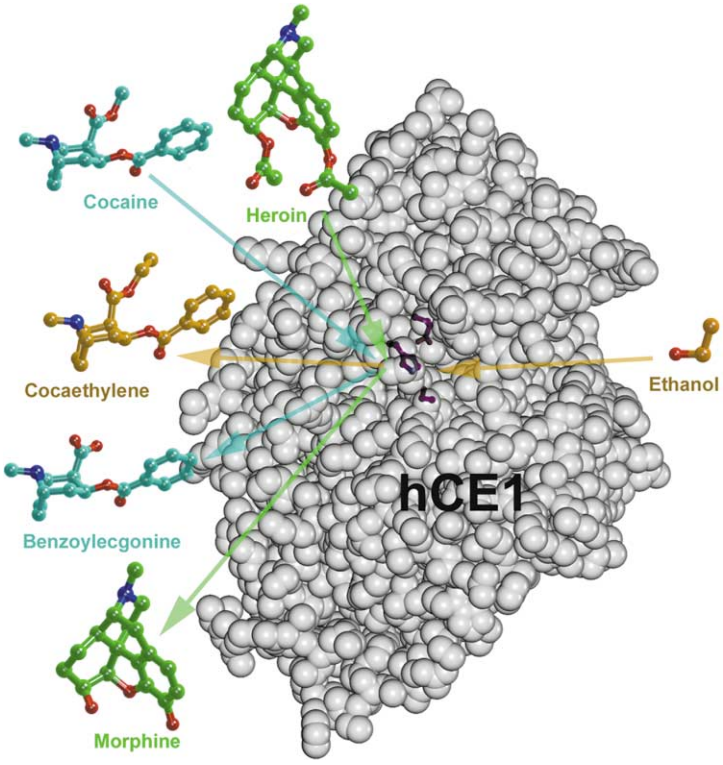

Figure 2. Human Carboxylesterase 1 Metabolizes Cocaine to Benzoylecgonine, and, When Alcohol Is Present, to Cocaethylene; the Enzyme Also Converts Heroin to Its Active Metabolite, Morphine

Benzoylecgonine, cyan; cocaethylene, gold; morphine, green. Both figures were provided by S. Bencharit and M.R. Redinbo, UNC-Chapel Hill.

exciting results with implications for drug design, the treatment of cocaine and heroin abuse, and victims of chemical warfare or terrorism.

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