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New Therapy for Cocaine Toxicity: Enzyme Break Downs Cocaine Into Inactive Products Nearly 1,000 Times Faster Than Human Body Does

Cocaine toxicity due to drug overdose results in more than half a million emergency room visits annually. Despite these alarming statistics, there is no Food and Drug Administration-approved pharmacotherapy specifically designed to treat cocaine toxicity. Emergency medical personnel are limited to treating only the immediate life-threatening symptoms of patients, while toxic levels of cocaine and its metabolic break-down products persist and continue to damage the cardiovascular system, liver and brain.

However, researchers have now developed and tested a modified enzyme that can break down cocaine into inactive products nearly 1,000 times faster than the human body does regularly. This engineered enzyme, called CocE, may be an excellent candidate for clinical use.

The difficulty in designing a therapy for cocaine toxicity stems from the drug's complex mechanism of action. Cocaine can block multiple targets in the brain and body, which accounts for this drug's cardiovascular and anesthetic effects, as well as its strong addictive properties. In addition, many of the metabolites of cocaine formed by the body (such as norcocaine and cocaethylene) have similar and sometimes stronger effects than cocaine itself.

Due to the myriad of action sites that would need to be blocked to eliminate the toxic physiological effects of cocaine and its by-products, the best strategy to treating toxicity from overdose is to directly eliminate the drug.

Remy L. Brim and colleagues at the University of Michigan, in collaboration with Columbia University and the University of Kentucky, have been researching the potential of cocaine esterase (CocE) to block cocaine toxicity by eliminating cocaine. CocE is an enzyme originally isolated from a soil bacterium found around the roots of the coca plant, that can break down cocaine into the same metabolites as the natural human enzyme butyrylcholinesterase, only much more rapidly.

CocE, however, is naturally unstable at the normal body temperature of 37°C. To enhance the thermal stability of

the enzyme, the investigators used a series of biochemical and computational approaches to modify the enzyme.

The thermally stable CocE was found to effectively degrade cocaine and two of cocaine's active metabolites, norcocaine and cocaethylene, and not degrade benzoylecgonine, the metabolite used in urinalyses for recent cocaine use. The researchers also evaluated CocE's ability to break down cocaine in the presence of drugs commonly co-abused with cocaine, and observed no reduction in CocE's action in the presence of alcohol, nicotine, and morphine, among others.

These promising results, in combination with previous studies that show CocE can reverse cocaine-induced cardiovascular changes, seizures, convulsions and lethality in rodent models, suggest that CocE may be a good candidate for clinical treatment of cocaine toxicity.

Brim will present this research, which was supported by the National Institutes of Health, the National Institute of Drug Abuse, and Reckitt Benckiser, at the American Society for Pharmacology and Experimental Therapeutics annual meeting in a poster titled "Ability of bacterial cocaine esterase to hydrolyze active cocaine metabolites, and function in the presence of commonly co-abused drugs."

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