

MEETING ABSTRACTS

DESIGN OF A BUTYRYLCHOLINESTERASE MUTANT FOR DETOXIFYING COCAINE AND ITS TOXIC METABOLITES IN CONCURRENT USE OF COCAINE AND ALCOHOL

Fang Zheng, Xirong Zheng, Ting Zhang, Xiabin Chen, and Chang-Guo Zhan

Department of Pharmaceutical Sciences, University of Kentucky, Lexington, KY, 40513, United States

Cocaine abuse is a major medical and health problem. There is no FDA-approved medication for treatment of cocaine overdose and addiction. Statistical data show that 92% of cocaine users also consume alcohol. The risk of immediate death is 18 - 25 times greater for cocaine co-ingested with alcohol than for cocaine alone. Alcohol can react with cocaine to get a series of toxic compounds in body including cocaine, cocaethylene, norcocaine, norcocaethylene and benzoylecgonine.

In combination of our “virtual screening of transition states” computational protocol and artificial intelligence, a novel approach was used to design BChE mutants as multiple functional cocaine hydrolases (mfCocHs) for treatment of toxicity caused by concurrent use of cocaine and alcohol. Comparing the kinetic parameters of *native human BChE* and *mfCocH* against cocaine as well as its four toxic/harmful metabolites (i.e. norcocaine, cocaethylene, norcocaethylene and benzoylecgonine) determined by us, the most effective mfCocH has at least a ~1000-fold improved catalytic efficiency against three of the substrates (cocaine, norcocaine, and cocaethylene), ~100-fold and ~10-fold improved catalytic efficiency against norcocaethylene and benzoylecgonine, respectively.

In vivo studies have revealed that the mfCocH can effectively hydrolyze cocaine and its four metabolites in rats produced from the concurrent abuse of cocaine and alcohol in both addiction and overdose models. The mfCocHs was powerful antidote to treat cocaine (w/ or w/o alcohol) induced toxicity, even from the lethal toxicity after co-administrated 1 g/kg alcohol (IP) and 180 mg/kg cocaine (IP), at any time point as long as the subject is alive before treatment.