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Novel enzyme therapies for treatment of Cocaine addiction and overdose

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It has been known that cocaine produces the toxic and physiological effects through not only cocaine itself but also norcocaine formed from cocaine oxidation catalyzed by microsomal cytochrome P450 3A4 in the human liver. In addition, majority of cocaine users also consume alcohol, and alcohol can react with cocaine to produce cocaethylene which is significantly more cytotoxic than cocaine. Hence, a truly valuable cocaine-metabolizing enzyme for cocaine abuse/overdose treatment should be efficient for not only cocaine itself, but also its toxic metabolites including norcocaine and cocaethylene. The catalytic parameters (k_{cat} and K_M) of human butyrylcholinesterase (BChE) and various mutants (including the one which is under clinical trial for cocaine addiction treatment) for norcocaine and cocaethylene have been characterized in the present study in comparison with those for cocaine. Based on the obtained kinetic data, wild-type human BChE has a lower catalytic activity for norcocaine and cocaethylene compared to its catalytic activity for cocaine. The BChE mutants have considerably improved catalytic activity against norcocaine and cocaethylene compared to the wild-type BChE. One of the BChE mutants, denoted as E12-7, is identified as the most efficient enzyme for hydrolyzing norcocaine and cocaethylene in addition to its high activity for cocaine. E12-7 has a 2020-fold improved catalytic efficiency for cocaine, a 1080-fold improved catalytic efficiency for norcocaine, an 861-fold improved catalytic efficiency for cocaethylene, and a 10-fold improved catalytic efficiency for benzoylecgonine. It has been demonstrated that E12-7 as an exogenous enzyme can indeed rapidly metabolize cocaine, norcocaine and cocaethylene in rats.

Biography

Fang Zheng has completed her PhD from Huazhong University of Science and Technology and Post-doctoral training in University of Kentucky. She is currently an Associate Professor at Department of Pharmaceutical Sciences at College of Pharmacy, University of Kentucky. She has published more than 88 papers in reputed journals and has more than 10 patents. She was the winner of 2014 AAPS (American Association of Pharmaceutical Sciences) Innovation in Biotechnology Award.

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