Effects of Exogenous Cocaine Hydrolases on Metabolic Profile of Cocaine in Rats
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Purpose
Enzyme therapy using a highly efficient exogenous cocaine-metabolizing enzyme is recognized as a promising new therapeutic strategy for cocaine abuse. Our recently designed cocaine hydrolases (CocHs), engineered from human butyrylcholinesterase (BChE), have a considerably improved catalytic efficiency against cocaine. In this study, we want to know whether CocHs are active in vivo for accelerating cocaine metabolism. Based on the in vivo data, we may select the CocH with the best overall in vivo profile for further animal behavior studies.

Methods
CocHs were produced in a bioreactor using stable cell lines that we developed previously, and were purified. The purified CocHs were used to test their actual in vivo activities in metabolizing cocaine in rats.

Results
We have successfully prepared and characterized a set of high-activity CocHs, including CocH3 (A199S/F227A/S287G/A328W/Y332G mutant of human BChE). According to the in vivo data, even a tiny dose of CocH3 (0.15 mg/kg, i.v.) can dramatically change the metabolic profile of cocaine. Without the CocH3 administration, the dominant cocaine-metabolizing pathway in rats was cocaine methyl ester hydrolysis to benzoylecgonine. With the CocH3 administration, the dominant cocaine-metabolizing pathway in rats became cocaine benzoyl ester hydrolysis to ecgonine methyl ester, and the other metabolic pathways became insignificant.

Conclusion
The animal data suggest that CocH3 has the desirable in vivo catalytic activity for accelerating cocaine hydrolysis in rats. Hence, CocH3 could be developed further to become the desirable enzyme therapy for cocaine addiction treatment.

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