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Are Pharmacokinetic Approaches Feasible for Treatment of Cocaine Addiction and Overdose?

Fang Zheng, Dr. and **Chang-Guo Zhan, Dr. [Professor]**

Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, 789 South Limestone Street, Lexington, KY 40536, USA, TEL: 859-323-3943, FAX: 859-323-3575

Chang-Guo Zhan: zhan@uky.edu

Abstract

"… we discuss the main challenges for developing therapeutic treatment of cocaine addiction and explain why pharmacokinetic approaches, particularly those based on our recently developed efficient cocaine-metabolizing enzymes, are feasible for treatment of cocaine addiction and overdose."

Keywords

Pharmacokinetic agent; therapeutic enzyme; drug abuse; drug overdose; drug addiction; drug metabolism

Cocaine addiction and overdose are major medical and public health problems that continue to defy treatment.[1] Generally speaking, pharmacological treatment for drug abuse can be either pharmacodynamic or pharmacokinetic. The traditional pharmacodynamic approaches to cocaine addiction treatment include possible medications to target a specific subtype of transporters/receptors, which affect various neurotransmitter systems, such as dopaminergic, serotoninergic, noradrenergic, cholinergic, glutamatergic, GABAergic, and opioidergic pathways, and modulate neurological processes. However, despite of decades of effort, pharmacodynamic treatment of cocaine abuse has been proven very elusive.[2] There is still no FDA (U.S. Food and Drug Administration)-approved medication available. The inherent difficulties in antagonizing cocaine in central nervous system (CNS) have led to the development of protein-based pharmacokinetic approaches using an enzyme, antibody, or vaccine, with an aim to alter the pharmacokinetics of cocaine in a favorable manner by tightly binding or rapidly metabolizing cocaine. Below we will briefly discuss the main challenges for developing therapeutic treatment of cocaine addiction and explain why pharmacokinetic approaches, particularly those based on our recently developed efficient cocaine-metabolizing enzymes,[3,4,5,6,7,8] are feasible for treatment of cocaine addiction and overdose.

Correspondence to: Chang-Guo Zhan, zhan@uky.edu.

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Why can cocaine addiction be an extremely difficult habit to break? Why has it been so difficult to develop an effective anti-cocaine medication? As well known, the primary effect of cocaine on the nervous system is that cocaine blocks the reuptake of monoamines, including dopamine (DA), serotonin (5-HT), and norepinephrine (noradrenaline, NA), by blocking the respective transporters. To simplify the discussion here, let us focus on the primary transporter, *i.e*. dopamine transporter (DAT), as a typical example for the effects of cocaine. Cocaine binds with DAT in the same binding pocket as dopamine.[9] As a result of cocaine blocking dopamine reuptake, the short-term effects of cocaine include feeling "good" because there are more dopamine molecules in the synapse for signaling. As one of the unwanted long-term effects, cocaine addiction is associated with cocaine-induced change in the brain's communication system, including the rapid upregulation of DAT expression on the cell surface. One-time use of cocaine will increase the surface DAT expression for at least a month, as normalization of dopaminergic function is usually an extremely slow process.[10] Due to the increase of the surface DAT expression, there are less dopamine molecules available in the synapse for signaling, which may contribute to the drug seeking or carving.

Generally speaking, solving a drug addiction problem always needs to account for two aspects: antagonizing the stimulant effect of the abused drug, and bringing the function of brain's communication system back to normal. These two aspects are closely related to each other for cocaine abuse. It would be very difficult to bring the function of brain's communication system back to normal, without effectively antagonizing the stimulant effect of cocaine. This is because whenever cocaine is used, cocaine will increase the surface DAT expression for at least a month[10] such that the function of brain's communication system cannot be normal for at least a month. So, it is necessary to first antagonize the stimulant effect of cocaine for cocaine addiction treatment. Under that condition, one can have a better chance to bring the function of brain's communication system back to normal.

How can we antagonize the stimulant effect of cocaine without blocking the normal function of DAT? It is extremely difficult to directly block cocaine binding with DAT without blocking the normal function of DAT, because cocaine and dopamine bind with DAT in the same binding pocket as mentioned above.[9] Pharmacokinetic approach provides an alternative, more realistic option to antagonize the stimulant effect of cocaine without blocking the normal function of DAT and other transporters/receptors in the nervous system. Pharmacokinetic antagonism of cocaine could be implemented by using either a cocaine-binding molecule, such as a cocaine antibody, which binds tightly to cocaine so as to prevent cocaine from crossing the blood-brain barrier (BBB), or an efficient cocaine-metabolizing enzyme which can quickly transform cocaine into biologically inactive metabolites in plasma such that no cocaine molecules can reach the CNS.[11] The antibody approach may be implemented through either active prophylaxis (vaccine)[12,13] or passive prophylaxis (monoclonal antibody produced in another host).[14] A cocaine-metabolizing enzyme may be provided through either enzyme therapy (in which the therapeutic agent is an exogenous enzyme)[3–8,16] or corresponding gene therapy (in which the therapeutic agent is the cDNA in an appropriately selected vector).[15] An appropriately designed pharmacokinetic agent is not expected to cross the BBB and, thus, can be realistically expected to antagonize the

stimulant effect of cocaine without blocking the normal functions of DAT and other transporters/receptors.

Why is an efficient cocaine-metabolizing enzyme promising for treatment of cocaine addiction? While it should be recognized that all of the above-mentioned pharmacokinetic approaches have their own advantages, the use of a cocaine-metabolizing enzyme has a major advantage over antibody or vaccine approach in terms of the efficiency. In particular, an antibody binds stoichiometrically with cocaine. The antibody or vaccine approach is expected to work well when the drug concentration is low in plasma. However, when the molar concentration of cocaine is significantly higher than that of the available antibody in plasma, the antibody would be saturated by cocaine such that most of the cocaine molecules are still free for their actions, even if the cocaine-binding affinity of the antibody could be infinitely high. Thus, the actual efficacy of the antibody or vaccine approach is dependent on the molar concentration of antibody available in plasma.

In comparison, a cocaine-metabolizing enzyme will also be saturated in the case of high cocaine concentration. For a remarkable difference, an enzyme molecule can not only bind with, but also degrade, a cocaine molecule. Each enzyme molecule can degrade many cocaine molecules, depending on the turnover number (catalytic rate constant k_{cat}) and Michaelis-Menten constant (K_M). For example, one of our designed and discovered cocaine hydrolases (CocHs) is the A199S/F227A/S287G/A328W/Y332G mutant[4] of human butyrylcholinesterase (BChE) with k_{cat} = 5,700 min^{-1} and K_M = 3.1 μM, indicating that each of the enzyme molecules can hydrolyze up to 5,700 cocaine molecules per minute. Further *in vivo* studies in mice (Xue, Hou, Fang, Zheng, and Zhan, unpublished data) revealed that pretreatment with the A199S/F227A/S287G/A328W/Y332G mutant (5 mg/kg, i.v., 1 min before cocaine administration) completely blocked 90 mg/kg (i.p.) cocaine-induced locomotor activity. So, a high-activity enzyme can be expected to completely/effectively block cocaine from reaching the brain to produce detectable physiological effects.

Why is an efficient cocaine-metabolizing enzyme feasible for treatment of cocaine overdose? Cocaine overdose occurs after the user takes the drug with a dose higher than his/her body can tolerate. According to Drug Abuse Warning Network (DAWN) report on National Estimates of Drug-Related Emergency Department Visits, cocaine is the most commonly involved drug for emergency department (ED) visits involving illicit drugs. The total number of cocaine-involved ED visits in 2007 within the United States was estimated to be 553,530 (CI: 382,646 to 724,414), accounting for ~57% of all illicit drug-related ED admissions seeking immediate medication. Although cocaine has a variety of physiological and psychological effects, including delirium, anxiety, panic, agitation, convulsion, and hyperthermia, cocaine-associated chest pain is the most commonly reported reason for the ED visit. Cocaine-induced chest pain is related to the considerable increase in the mean arterial pressure (MAP) and heart rate (HR) caused by cocaine. Cocaine existing in the body will continuously cause damages through affecting the heart and respiratory system *etc*. by considerably increasing the MAP and HR. Obviously, the most effective approach to cocaine overdose treatment will be to quickly metabolize cocaine in the body by administration of an exogenous enzyme. The MAP and HR will return to normal after cocaine is cleared up in the body, as demonstrated in monkeys.[16]

Concerning the feasibility of cocaine overdose treatment using an exogenous enzyme, one may have a couple of fundamental questions concerning the feasibility of the enzyme approach for cocaine overdose treatment. *What is the half-life of cocaine in the body under the overdose conditions? How can exogenous enzymes clear up cocaine molecules that have already reached the CNS before the enzyme is injected, now that the exogenous enzyme does not reach the CNS?* Concerning the first question, it has been known that the cocaine half-life in the body is linearly proportional to the dose of cocaine.[17] So, under cocaine overdose conditions, the cocaine half-life is actually very long, much longer than that observed in usual animal studies with a low dose of cocaine. Concerning the other question, as demonstrated in the positron emission tomography (PET) imaging studies,[18] cocaine distribution in the body can reach the equilibrium among the plasma, brain, and heart *etc*. in few minutes. Thus, cocaine molecules can rapidly cross the BBB from plasma to brain and from brain to plasma. When cocaine molecules in plasma are metabolized, cocaine molecules in brain (and heart *etc*.) can readily return to plasma in order to keep the thermodynamic equilibrium.

How soon can we expect to have enzyme-based therapies available for practical treatment of cocaine addiction and overdose in humans? In light of extensive studies in animal models of cocaine overdose and addiction using mice, rats, and monkeys, two types of enzymes have been recognized promising for cocaine addiction and overdose treatment: one is our rationally designed and discovered high-activity mutants of human BChE[3–6] that have been recognized as the true CocHs;[19] the other is the thermostable mutants of bacterial cocaine esterase (CocE) that were also discovered through integrated computational-experimental studies.[7,8,16] The rights of the thermostable CocE mutants for cocaine overdose treatment[8] have been licensed to Reckitt Benckiser Pharmaceuticals Inc from a consortium consisting of scientists from three universities (Columbia University, University of Kentucky, and University of Michigan). All of the technology transfer and investigational new drug (IND)-enabling studies on the T172R/G173Q mutant of CocE have been completed, and the IND application has been filed with FDA.

The first one of our designed, discovered, and patented CocHs, *i.e.* the A199S/S287G/A328W/Y332G mutant of human BChE,[3,6] has been fused with human serum albumin.[19] The albumin-fused A199S/S287G/A328W/Y332G mutant has been known as Albu-CocH or TV-1380 or AbluBChE which is currently in double-blind, placebo-controlled clinical trials by Teva Pharmaceutical Industries Ltd for cocaine addiction treatment.[20] The initial trial in 40 cocaine recreational volunteers has revealed that the enzyme is safe and efficacious for humans; the enzyme administration decreased the cocaine liking, the desire to take cocaine again, and the overall drug liking.[20]

In summary, the pharmacokinetic approaches, particularly those using an efficient cocaine-metabolizing enzyme, are indeed promising for treatment of cocaine addiction and overdose.

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Biographies

Dr. Fang Zheng

Dr. Chang-Guo Zhan

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