

## Commentary

## Thinking Outside the Synapse: Pharmacokinetic-Based Medications for Cocaine Addiction

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Cocaine addiction persists as a significant public health problem for which no FDA-approved medications currently exist. Two papers published in this issue of *Neuropsychopharmacology* illustrate progress being made using a pharmacokinetic approach to the treatment of cocaine addiction and cocaine overdose. In contrast to the traditional medications that focus on small-molecule receptor agonists or antagonists to block or render the brain less sensitive to the direct pharmacological actions of cocaine, the pharmacokinetic approach aims to substantially decrease the concentration of cocaine that reaches the brain in the first place.

One approach to reducing circulating concentrations of cocaine is to increase enzymatic metabolism. Over the last decade, James Woods *et al* have characterized a bacterial cocaine esterase (CocE) originally discovered in bacteria that live in the soil around coca plants that use cocaine produced by the plant as a source of carbon and nitrogen. A thorough series of studies demonstrated the ability of CocE to attenuate various toxic effects of cocaine. Particularly impressive was the demonstration, in rats, that CocE could prevent death even when administered *after* an otherwise lethal dose of cocaine (Jutkiewicz *et al*, 2009; Wood *et al*, 2010). Although encouraging results have been generated with other cocaine-metabolizing enzymes including butyrylcholinesterase, CocE was found to have superior efficiency and selectivity.

These data firmly established CocE as a potential emergency-room treatment for cocaine overdose. However, the half-life of the CocE was far too short to be developed as a prescribed medication to reduce ongoing use of cocaine in dependent individuals. Subsequently, a mutant CocE (PEG-CCRQ CocE) was developed that retains the capability of the parent enzyme to block the lethal cardiovascular and seizure-inducing effects of cocaine, but with a half-life

measured in days rather than minutes. In this issue of *Neuropsychopharmacology*, Collins *et al* (2011) demonstrate the effectiveness of PEG-CCRQ CocE in animal models of cocaine abuse considered to have the best predictive validity with respect to measuring the abuse liability of drugs: drug discrimination and intravenous self-administration. In a series of thorough experiments, the authors convincingly demonstrate that administration of PEG-CCRQ can shift cocaine self-administration and discrimination dose-response curves significantly rightward for up to 72 h. Furthermore, the mutant CocE did not alter the cocaine-like interoceptive effects of methylphenidate or *d*-amphetamine, whose mechanisms of action are nearly identical to that of cocaine. Thus, these experiments demonstrate not only effectiveness and a prolonged duration of action, but also pharmacological selectivity.

Also in this issue, Wee *et al* (2011) report on progress in the development of a vaccine that would promote active immunization against cocaine. As small molecules such as cocaine cannot elicit an immune response, cocaine-like analogs must be first coupled with a larger carrier molecule. Previous attempts have linked cocaine-like haptens (such as TA-CD, GNC, and GND) to relatively neutral carriers (PBS) or proteins that enhance the host's immune response such as keyhole limpet hemocyanin or recombinant cholera B toxin (rCTB). Wee *et al* (2011) coupled a 'third generation' hapten (GNE) that has a more potent immunological profile than previous analogs with a more potent carrier/adjuvant, a disrupted serotype 5 adenovirus vector (dAd5). Rats were vaccinated with dAd5GNE or non-conjugated dAd5 (control) and boosted, depending on the experiment, two or three times. Vaccinated animals showed anti-cocaine effects in several standard behavioral assays. The dAd5GNE vaccine prevented cocaine-induced locomotor sensitization and shifted the dose-response curve for intravenous cocaine self-administration on a fixed-ratio 1 schedule downward. Also, vaccinated rats responded to lower breakpoints on a progressive-ratio (PR) schedule than controls.

The attenuation of the behavioral effects of the dAd5GNE vaccine is explained by alterations in the distribution of cocaine. As the antibodies do not cross into the brain,

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antibody-bound cocaine is effectively sequestered in the periphery. Wee *et al* (2011) demonstrated such a phenomenon by injecting [ $^3\text{H}$ ]-cocaine intravenously and killing the animals 2 min later. A 66% reduction in the levels of [ $^3\text{H}$ ]-cocaine in the brains of immunized rats was observed compared with control rats. By contrast, levels of cocaine in the serum were increased several fold, indicating that cocaine had been effectively retained in the blood. It appears that the vaccine adds an additional peripheral compartment that buffers against fast-rising drug levels in the brain. Rapid onset of drug action is critical for addiction-related behavioral effects. Behavioral sensitization produced by intravenous cocaine and escalation of breakpoints on a PR schedule (Samaha *et al*, 2004; Liu *et al*, 2005) have both been shown to be sensitive to the speed of drug injection, and slowing cocaine's entry into the brain would be expected to reduce the euphorogenic effects (de Wit *et al*, 1992).

The active immunization strategy requires the production of a sufficient (yet to be determined critical) binding capacity in sera. Of course high antibody titers are essential but titers do not necessarily reflect binding capacity for the drug. Titers reflect the detection of antibodies created to the hapten-carrier complex; the antibody may or may not have a high affinity for binding cocaine itself. Wee *et al* (2011) report a  $K_D$  for cocaine of 5–100 nM. Gentry *et al* (2009) have suggested, based on preclinical studies with monoclonal antibodies targeting methamphetamine, that  $K_D$  values in the lower nM range should be adequate. Comparison of total binding capacity produced by new vaccines and adjuvants should help define minimum values required to blunt drug onset times and reduce specific behavioral responses.

These two papers highlight the promise of pharmacokinetic-based medications for cocaine addiction distinct from the design of small molecules that act in the brain. Challenges remain however; these include the design of longer lasting (perhaps sustained-release) formulations of cocaine-metabolizing enzymes and maximization of the binding capacity achieved with active vaccination. In addition, these approaches may face challenges to FDA approval that are not shared by small-molecule pharma-

cotherapies. However, the papers in this issue represent a significant advance in reporting considerable success in antagonizing the effects of cocaine-using animal models that are considered the gold standard in assessing the abuse liability of cocaine.

## DISCLOSURE

The authors declare no conflict of interest.

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