Published in final edited form as:
Hum Vaccin. 2009 April ; 5(4): 194–199.

Vaccines for Cocaine Abuse

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Abstract

Treatments for cocaine abuse have been disappointingly ineffective, especially in comparison with those for some other abused substances. A new approach, using vaccination to elicit specific antibodies to block the access of cocaine to the brain, has shown considerable promise in animal models, and more recently in human trials. The mechanism of action for the antibody effect on cocaine is very likely to be the straightforward and intuitive result of the binding of the drug in circulation by antibodies, thereby reducing its entry into the central nervous system and thus its pharmacological effects. The effectiveness of such antibodies on drug pharmacodynamics is a function of both the quantitative and the qualitative properties of the antibodies, and this combination will determine the success of the clinical applications of anti-cocaine vaccines in helping addicts discontinue cocaine abuse. This review will discuss these issues and present the current developmental status of cocaine conjugate vaccines.

Keywords

Substance Abuse; Vaccine; Cocaine; Immunization; Antibody; Conjugate

INTRODUCTION

Substance abuse contributes to many of the social ills that plague almost every country in the world. The distribution and sale of illegal addictive drugs have become huge criminal enterprises that provide the impetus for the victims of addiction to pursue illegal activities, leading to theft, robbery, assault, prostitution, and motor vehicle accidents. This results in ancillary problems in families, jobs, and schools and affects the larger community around every individual. For example, of all federal and state prisoners who had committed property crimes, more than 30% were convicted of offenses directly relating to their efforts to obtain money for drugs.[1] Increased use of addictive drugs has occurred around the globe, in both developed and newly emerging economies.[2–4] Billions of dollars have been spent in the United States for the interdiction of drug importation, prevention of local drug production, and imprisonment of drug users and dealers.[5] However, the principal effect of these efforts has been to provide price supports for these illegal substances, enhancing their value to those who grow or produce them,

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as well as to the subsequent processors and distributors. It should be clear that addicts' drug behavior cannot be prevented simply by declaring the addicting substances illegal, and imposing Draconian penalties for their possession and use.[6] As a result, it is imperative to pursue other methods of helping substance abusers discontinue their use of addictive drugs.

In 2007, up to 14% of people over the age of 12 in the United States had used cocaine at least once, and of those, 2.3% had used the drug within the past year, almost a million of them for the first time.[7] However, among 12th graders, use is alarmingly higher with almost 8% admitting to use in the past year, and 2% within the prior month.[8] As the baby boom generation enters the elderly population, even this age group may have substantially increased numbers of drug abusers in the near future[9]. The negative consequences on the education, employment, health, and behavior of both young and old people can be overwhelming.[5, 9] Although the data is less well documented, the level of abuse for cocaine in other countries is thought to be similar to that in the United States,[10] and thus approaches to treat addiction are needed that can be global in application. Not all individuals transiently exposed to cocaine will become addicted, but once addiction occurs, breaking the cycle of dependence is very difficult for most victims, with dropout rates from treatment programs of various kinds exceeding 50%.[11] This occurs because even when an addict can get past the withdrawal symptoms of dysphoria, fatigue, irritability, appetite changes, and insomnia, the susceptibility to relapse from intense drug craving becomes still higher.[12–14] Drug substitution therapy, as is common in western countries for some addictions,[5, 15] is not feasible for cocaine at present, and other pharmacological treatment efforts have thus far met with very limited success.[14] Even if a drug is eventually developed for such treatment approaches, it would likely be too expensive for use in many less developed countries, as has been the case for methadone in heroin addiction.[16] An entirely different avenue to achieve a persistent reduction in the reinforcement mechanism resulting from cocaine re-exposure might be achieved by blocking the entry of the drug into the brain. This blockade could be achieved with antibodies elicited by a therapeutic vaccine, because IgG-bound drug cannot readily cross the normal, uninflamed blood-brain barrier. To utilize this approach to cocaine addiction effectively will require a thorough understanding of the mechanisms of antibody blockade and the immunological parameters that govern both the development and persistence of antibody responses, as well as the influence of antibodies on the pharmacodynamics of cocaine. Hence this review will discuss the pertinent aspects of the immune response to hapten conjugate vaccines, animal studies involving cocaine vaccines, and the current status of clinical vaccines. The development of a human vaccine capable of blocking the pharmacologic action of cocaine on the brain has great potential as part of a therapeutic program to enable motivated cocaine addicts to escape from the devastating consequences of their addiction.

REGULATION OF IMMUNE RESPONSES TO HAPTEN CONJUGAGE VACCINES

The immunological response to foreign antigen exposures is a tightly regulated phenomenon that ensures that the resulting effector molecules and cells usually eliminate or neutralize the antigen (and/or associated pathogen) with a minimal amount of tissue damage. For small molecules like cocaine or other abused drugs, the effector mechanism is essentially restricted to antibodies, given the extraordinarily rapid pharmacodynamics of these agents.[17] As discussed below in more detail, antibodies are capable of very rapid binding in solution phase at physiological temperatures, and if the antibodies are present in sufficient quantity while also capable of binding tightly, most of an ordinary dose of cocaine could be bound in circulation before it has a chance to cross the blood-brain barrier.18 Unfortunately, this amount of antibody is well above that elicited by the most vaccines given to protect against microbiological pathogens, such as the 1–2 μg/mL of specific antibody which is sufficient to prevent tetanus.19 Hence, optimization of vaccine design and administration by exploitation of the modern

understanding of immunoregulation will be essential to achieve the goals of successful conjugate vaccines for substance abuse.

High level antibody responses to haptens (small molecules capable of being recognized by the immune system) require conjugation of the hapten to another substantially larger molecule that can function as a "carrier", enabling the hapten to be effectively presented to the immune system. Otherwise, even though some B cells will, on the basis of the random recombination events that govern the development of initial B cell antibody receptor specificity, be capable of binding a specific small molecule like cocaine, little or no positive cellular activation will occur from binding of the antibody displayed on the B cell surface since there is no cross linking of these surface antibodies.[20] In order to stimulate the B cell program of clonal growth, specific antibody production, and affinity maturation, T cell activation is essential to provide help for B cell stimulation and development. T cell function in this regard serves multiple critical processes that regulate the appropriate production of antibodies. The coordinated dual nature of immune activation ensures a high likelihood of specific antigen recognition, reducing inappropriate production of antibodies that might recognize self antigens and lead to autoimmune disease, or development of antibodies against chemicals needed for metabolism. Coincidentally, this enables small molecules to be widely utilized as medicines or chemical components of foods that we eat without a high incidence of immune responses to them.

However, the immune system does have the potential to malfunction and react against small molecule haptens. It is instructive to consider how this occurs, since, as discussed above, the hapten itself should not capable of eliciting this response. Penicillin is the classic example of this malfunction, since a small minority of patients who receive penicillin develop severe allergic responses to it. Penicillin and its metabolites can bind to native proteins in the body, creating conjugate molecules21 that fortunately function as a very poor immunogens in most people. In susceptible individuals, however, IgE can be elicited, sensitizing them to any future penicillin exposures with disastrous results such as anaphylaxis. In the context of cocaine, detectable antibodies,[22] some of the IgG type (Martell, et al., 2008 submitted) have been observed in the serum of some addicts. Whether this is due to the actual conjugation of cocaine to native proteins in humans, as has been demonstrated in vitro and in animal models,[22] or due to the complex mixture of contaminated materials that addicts can sometimes inject or inhale is not known. Nonetheless, the incidence of true allergy to cocaine has not been recorded other than occasional reports of vasculitis23, 24 sometimes attributed to the said complex mixture of crude materials bought on the street.25 Given the widespread abuse of this drug around the world, the absence of significant evidence for allergic reactions to cocaine suggests that allergy must be rather rare, as it is for other substances of abuse, like opiates.[26, 27] As discussed further below, the intentional conjugation of cocaine to effective carriers for vaccine purposes has not resulted in clinical allergic reactions in either animals[28–30] or humans,[31, 32] and so this risk appears to be quite small.

IMMUNOLOGICAL GOALS FOR A COCAINE VACCINE

As mentioned above, the quantity of IgG elicited by a conjugate vaccine for cocaine will have to be substantially higher than the amount of antibody stimulated by ordinary vaccines against microbes or toxins like influenza or tetanus. Jenkins[17] demonstrated that smoking cocaine leads to 0.5 μM concentrations of cocaine in the blood and results in typical pharmacological effects in experienced drug users. This peak concentration occurs within minutes of drug delivery, and from animal studies as well as from studies of the observable pharmacological effects of the drug in humans, it is clear that much of the transfer of cocaine to the CNS also occurs within minutes.[17] Both the number of receptors occupied in the brain and the rate at which these receptors are occupied influence the pleasure and reinforcing pharmacological effects[33] that determine the psychological experience from the drug's use. Thus, in order for antibodies to

keep cocaine out of the central nervous system by binding it in circulation, the "on" rate of binding must be similarly rapid to prevent accumulation of the drug in the brain. Fortunately, the binding rates of hapten molecules to antibodies to have been well studied in the past,[34, 35] and the rates are such that when haptens and antibodies are thoroughly mixed in solution, complete binding of haptens to high affinity antibodies occurs in seconds,[36] quite adequate for the purposes of a cocaine vaccine. The combination of the on and off rates of binding determine the affinity of the antibodies for their target, with highly avid antibodies having slow off rates.[36] The theoretical details of this interaction are discussed in more detail elsewhere,[37] but in brief, the intrinsic binding affinity of the isolated combining site (Fab) of an IgG antibody for a single cocaine molecule is the equilibrium constant (Kai) as described by the following equation where [Coc-Fab] is the concentration of drug/antibody complex, [Coc] is the free cocaine concentration, and [Fab] is the concentration of the unbound antibody fragment having the singe antigen recognition site.

$$K_{ai} = \frac{[Coc - Fab]}{[Coc][Fab]}.$$

The actual binding behavior, however, is modified by the fact that the two antibody combining sites of the IgG molecule act independently. This results in the following equations where Ka_1 is the affinity constant for binding to an unoccupied IgG molecule, and Ka_2 that for binding to an IgG that already has one occupied site:

$$Ka_1 = \frac{[Coc - IgG]}{[Coc][IgG]} \quad \text{and} \quad Ka_2 = \frac{[Coc - IgG - Coc]}{[Coc - IgG][Coc]}.$$

The values of these two affinity constants have been shown to be related to the intrinsic affinity constant[38] Kai by a factor of 2 as follows:

$$Ka_1 = 2 \times Kai \quad \text{and} \quad Ka_2 = Kai/2$$

Ka_1 operates at low drug concentrations, while binding to the second site will occur at higher drug concentrations with half the intrinsic affinity. Due to the expected concentrations of drug and antibody as discussed above, Ka_2 will dominate the behavior of the interaction.

As mentioned above, the concentrations of free drug-binding antibodies that will have to be achieved with substance abuse vaccines are substantially higher than the concentrations of antibodies ordinarily elicited by antimicrobial vaccines. For example, tetanus toxoid vaccine can completely protect against tetany with a specific antibody concentration of 1–2 μg/mL or higher.[19] Similar or even lower antibody concentrations have been found to be protective against other diseases.[39] In contrast, the concentration of a IgG antibodies in the plasma capable of binding 80% or more of a peak concentration of a pharmacologically active dose of cocaine would have to be at least 40 μg/mL (0.256 μM of antibody, with 2 combining sites per molecule),[18] assuming a reasonable average binding affinity for the antibodies. Thus most of the IgG antibody present would have to be utilized and its effective binding affinity for much of the drug would be equal to Kai/2. Figure 1 illustrates this issue, in which the amount of bound drug in a range of peak concentrations is presented. At the 0.5 μM cocaine level an average Ka_2 for IgG of 20 L/μM could bind 85% of the drug, while 98% would be bound for antibodies with a Ka_2 of 200 L/μM. These affinities are reasonably within the expected range for secondary antibody responses to haptens.[40] The proportion of bound drug for such an amount of antibody decreases, as expected, for higher cocaine concentrations, and falls almost linearly when the peak concentration of the drug is above 1 μM. While it is not clear yet exactly

what proportion of active drug needs to be bound in order to reduce its pharmacological effects, both the human and the experimental animal studies indicate that approximately 80% binding is a realistic and achievable estimate for efficacy. However, it is also well established that the rate of increase in receptor occupation in the CNS has a profound influence on the subjective effects of these drugs.[33] Thus, a less dramatic proportion of drug binding in circulation, e.g., 50%, might still have a substantial influence on the rate of entry of free drug into the CNS. Even if the eventual total accumulation in the brain is similar to what would be achieved in the absence of antibody, the subjective CNS effects of the drug might be substantially or completely blunted, since the rate of receptor occupancy would be significantly reduced.

PHARMACOKINETICS OF DRUGS AND ANTIBODIES

Initial blocking of single dose drug effects is certainly a primary goal for drug vaccines that seek to help addicts stay off the abused substance by inhibiting the dramatic reinforcement of drug seeking behavior that can occur from social stresses leading to cocaine exposure, especially in the early critical months after withdrawal.[41] Ideally, however, it would be useful to have the capacity to block multiple doses, especially during the days following such a challenge. Therefore, other issues of importance for cocaine abuse vaccines are the pharmacokinetics of the drug and the half life of the antibody after binding in circulation. It has been shown that the half life of an antibody bound to small hapten molecules, such as substance abuse drugs, is unaffected in an animal model.42 With regard to the half life of the drug itself, the issue is more complex and dependent on the specific properties and metabolites of the substance in question. For cocaine, it has been observed experimentally in animals that the drug half life in circulation remains nearly the same in the presence or absence of antibody, 43 suggesting that the metabolism of cocaine to benzoylecgonine in the bloodstream is not inhibited when the drug is bound to antibody. This is in marked contrast to the findings with methamphetamine specific antibodies44 or morphine specific antibodies,45 for which the half life of the drug in circulation is significantly prolonged in when bound to antibody. This makes cocaine a relatively ideal target for a vaccine, since the elicited antibodies might again be able to bind the active drug once the initial dose is cleared. However, it has not been directly demonstrated (to our knowledge) that the bound cocaine molecule, once metabolized to benzoylecgonine, is released from the polyclonal antibodies produced by vaccination; however, we and others have found that in sera from both experimental animals [28]and humans (Orson, unpublished) vaccinated against cocaine, benzoylecgonine is unable to inhibit specific antibody binding to cocaine except at concentrations up to 1000 fold higher than concentrations required for inhibition by free cocaine itself, even though the only difference between these molecules is that the methyl ester group of cocaine has been hydrolysed by plasma esterases. 46 (Figure 2). This changes the preferred molecular structure of the molecule, since benzoylecgonine exists as a zwitterion at physiological pH, in which the nitrogen's positive charge is counterbalanced intramolecularly by the negative charge on the carboxylic acid. Cocaine only has a relatively positive charge on the nitrogen when in solution, and presumably this difference in benzoylecgonine's charge and structure causes a poor binding affinity to anti-cocaine antibodies. It would seem likely that the structural change in benzoylecgonine would force release from the antibody, as is known to happen with a monoclonal antibody selected for its esterase activity.[47] As a result, even though heavy use of cocaine can result in plasma concentrations of benzoylecgonine up to 10 fold higher than the peak cocaine concentrations[48], the metabolite is unlikely to interfere with anti-cocaine antibody function. Some other minor cocaine metabolites are either structurally quite distinct, e.g., ecgonine methyl ester, or are present in only very low concentrations compared to cocaine itself, e.g., norcocaine.

Cocaine inhibits dopamine, norepinephrine, and serotonin reuptake,49 and thus the effects of the drug may be complex, with distinct effects at different concentrations of the drug due to a

differential influence on these neural pathways. Although there is little direct knowledge of such differences, George[50, 51] did observe paradoxical slowing of locomotor activity after very low dose administration (0.1 mg/kg, 1% of usual stimulatory dose), which we have also observed (Orson, unpublished), an effect that has been attributed to cocaine's influence on serotonin signaling.[50, 51] This observation may become important when dealing with a vaccine against cocaine, since it will be likely that even under the best of circumstances, a small amount of the drug may pass into the brain, potentially having such a pharmacological effect.

CLINICAL STATUS OF COCAINE VACCINES

With 2.4 million or more Americans age 12 or older as current users of cocaine,[5] the penetration of this problem is extensive, as all societal groups suffer from the health consequences and criminal behaviors that cocaine abuse engenders. A large fraction of cocaine addicts eventually seeks to discontinue their abuse as the consequences of the habit all too often become manifest, from criminal behavior to support the habit, to the health problems, such as acute coronary syndromes or worse. Unfortunately, despite a desire to quit, most addicted users are unable to stop using the drug, due to craving in the absence of cocaine and the reinforcement then elicited by cocaine use. Clinical treatments for cocaine addiction have been essentially limited to behavioral therapies that have had low success rates,[14] since there are no effective medications to treat this condition.

Animal immunization studies have demonstrated that high levels of antibody reduce uptake in the brain of rats and mice, block increases in cocaine induced locomotor activity, and more importantly for potential human interventions, inhibit reinstatement of cocaine self administration.[28, 30, 52, 53] As a validated model for substance abuse relapse, the latter is probably the most significant finding, since the predicted benefit of vaccination in humans would predominantly be to inhibit the reinforcement of craving that ordinarily results from any re-exposure to cocaine in the critical time after starting a period of abstinence.54 If one could substantially block the pleasurable effects of re-exposures and reduce the subsequent increased craving, it would help a great deal in preventing a resumption of regular drug use for those motivated users who succumb temporarily to the temptation of use brought on by social pressures or an individual stressful event. The immunization strategy for treating cocaine abuse in humans has progressed to the level of phase I and II trials using a vaccine consisting of cocaine conjugated to cholera toxin B (TA-CD),[32, 55] (Martell, et al., 2008 submitted). These trials have, in fact, shown considerable promise at the clinical level. The Phase I trial demonstrated the immunogenicity and safety of the TA-CD vaccine, showing significant antibody responses that were specific for cocaine,56 and this vaccine construct has been subsequently used in outpatient studies and was tolerated with no serious adverse effects during 12 months of follow-up[32, 53, 56] (Martell, et al., 2008 submitted). Another early trial demonstrated that, in a laboratory setting, the pleasurable effects of smoked cocaine administration could be inhibited, at least in those individuals with a relatively good antibody response.[32, 55] In the Phase IIa, 14 week trial of eighteen cocaine dependent subjects in early recovery, the vaccine was well tolerated at two dose levels (100 μg × 4 injections, or 400 μg × 5 injections), and cocaine specific antibodies persisted for at least six months.32 Furthermore, subjects who received the higher dose of vaccine had a significantly higher mean antibody titer and were more likely to maintain cocaine metabolite-free urines than the lower dose group.32

In a Phase IIb study with the TA-CD vaccine in 114 methadone clinic patients, substantial quantities of antibody were elicited in about one third of the vaccinated subjects, with IgG concentrations above 40 μg/mL (Martell, et al., 2008 submitted). Higher levels of antibody were correlated with periods of less cocaine use in a substantial number of these subjects, as determined by urine monitoring tests for benzoylecgonine, the major excreted cocaine metabolite. However, the level of antibodies induced in many subjects was considerably lower

than would be desirable, as indicated by the discussion above, demonstrating the need to improve the magnitude and consistency of the antibody responses. Of particular interest in these studies, some of the vaccinated patients had very low IgG responses to vaccination, and yet had substantial levels of anti-cocaine IgM antibodies at baseline, apparently induced by cocaine abuse (Orson, unpublished). Deng, et al.[22] previously reported detection of antibodies against cocaine in unvaccinated addicts, and demonstrated that adducts of cocaine with native serum proteins were likely to have formed in such individuals. Exactly how this may lead to relative vaccine unresponsiveness is an area of current investigation. A larger Phase IIb study is planned for TA-CD beginning in the winter of 2009 which should help answer some of these questions. Taken together, these results demonstrated that a cocaine specific vaccine can elicit an immunologic response sufficient to reduce cocaine usage and attenuate the self-reported psychological effects of cocaine. Of course, it is possible to override the effects of the vaccine by increasing the amount of cocaine used, and a few subjects did increase cocaine use even during the period when they had high antibody titers, as indicated by quantitative urine tests for benzoylecgonine. A cocaine vaccine will therefore be of use primarily for abusers who are motivated to quit, as mentioned previously. Other cocaine conjugate vaccines are still in the preclinical phase of development in our laboratory and elsewhere.

CONCLUSIONS

Cocaine has pharmacokinetic and pharmacodynamic characteristics that make it a viable target for vaccine development. On a theoretical basis, from the known properties of antibodies and the drug concentrations in blood expected in cocaine abuse, the quantity and quality of antibody that should be elicited by an efficacious vaccine must be sufficient to block drug effects, specifically by reducing and/or slowing the accumulation of the drug in the brain. Animal studies with cocaine vaccines have all shown promising results. Blocking immediate behavioral and toxic drug effects is valuable, but even more promising from the addiction perspective is the inhibition of drug reinforcement, or craving, which is necessary to help prevent resumption of drug use by individuals motivated to quit. According to some animal experiments, the inhibitory effects on reinforcement may not require levels of antibody blocking as high as would be expected for blocking of the acute drug effects, a property that could dramatically extend the benefits of this approach to therapy. Vaccination against cocaine should also very effectively complement current counseling programs and medications that may be developed in the future to treat this growing worldwide problem. Advances in vaccine conjugate design, carrier protein use, and especially adjuvant optimization are expected to significantly enhance the quantity and quality of the antibodies produced, allowing cocaine vaccines to become useful clinical tools for the treatment of this very difficult addiction.

Acknowledgments

Supported by the Department of Veterans Affairs (VA) Merit Review Program and VISN 16 Mental Illness Research, Education and Clinical Center (MIRECC), the VA National Substance Use Disorders Quality Enhancement Research Initiative (QUERI), and the National Institute on Drug Abuse grants K05 DA 0454 (TRK), P50-DA18197.

ABBREVIATIONS

CNS	Central Nervous System
Coc	Cocaine
Fab	Antibody fragment with one binding site
IgG	Immunoglobulin G
Kai	Equilibrium Intrinsic Affinity Constant

TA-CD Cholera Toxin B – Cocaine Conjugate Vaccine

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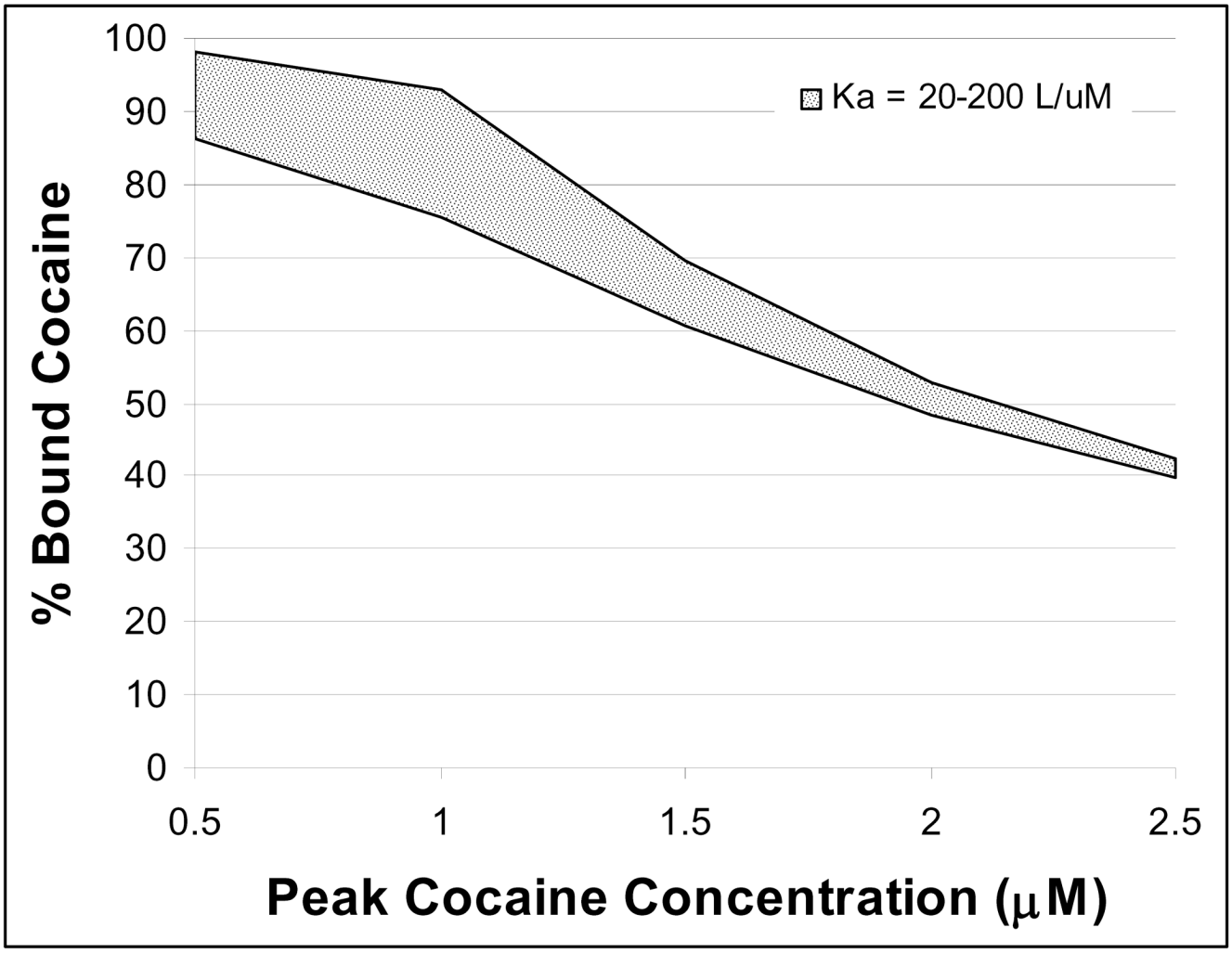

Figure 1. Drug Dose Effect on Binding for 20 to 200 μM^{-1} Ka_2 Affinity Antibodies

The amount of bound drug (Y axis) at equilibrium for different initial concentrations of drug (0.5 to 2.5 μM) is plotted against peak cocaine concentration (X axis) for 40 μg/mL of an antibody with a Ka_2 binding affinity of 20 μM^{-1} (bottom line of shaded band) or 200 μM^{-1} (top line of shaded band).

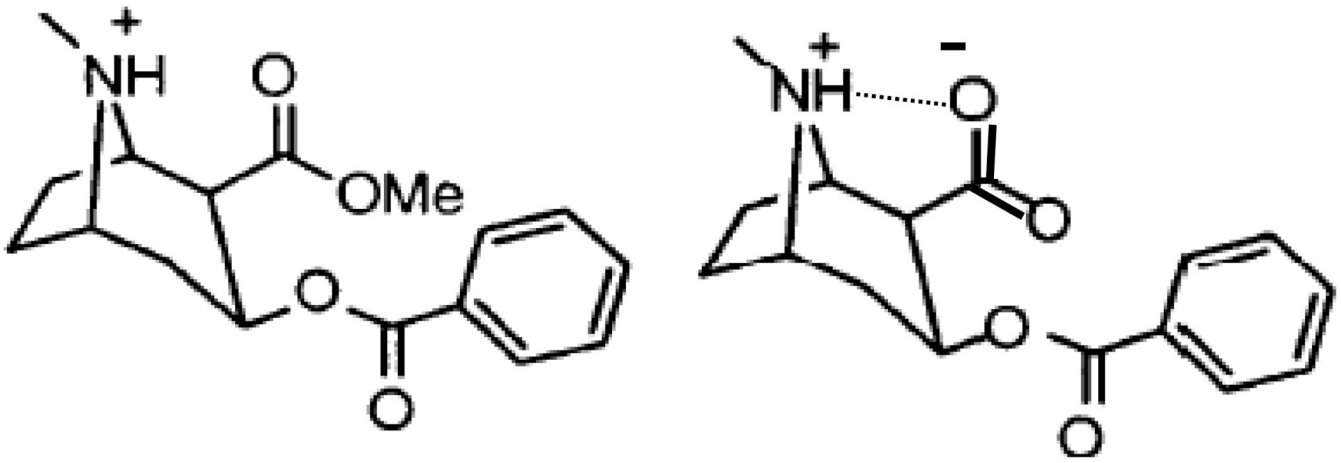

Figure 2. Cocaine and Benzoylecgonine Chemical Structures

Cocaine in physiological solution conditions has a relatively positive charge on its nitrogen (left), while hydrolysis of the methyl ester group results in benzoylecgonine (right) in which the positive charge on the nitrogen is intramolecularly balanced by a negative charge on the carboxyl group.