Antibodies as Pharmacokinetic and Metabolic Modifiers of Neurotoxicity

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INTRODUCTION

Abuse of psychoactive chemicals can result in neurotoxic effects that are difficult to treat medically. Successful therapy is often hindered by the lack of useful antagonists for many of these chemicals and by the extensive distribution of these chemicals out of the bloodstream. Although there are treatments for opiate addiction and an antagonist for opiate overdose, there are no such medical treatments for most drugs of abuse such as phencyclidine (PCP) and cocaine. Therefore, this chapter focuses on recent advances in immunotherapy which suggest this novel approach could be beneficial in the treatment of drug abuse.

PROBLEMS ASSOCIATED WITH TREATMENT OF PCP TOXICITY

PCP use by drug abusers sometimes results in behavioral toxicity that manifests as a wide variety of frightening effects that include extreme violence; self-destructive and psychotic behavior; and, at very high doses, even death (Peterson and Stillman 1978). Often the acute behavioral toxicity is not realized or even felt by the individual because of the anesthetic effects of the drug. Indeed, the lack of a pain sensation may contribute to PCP's ability to make users become violent and self-destructive. The acute toxicity of PCP is often misdiagnosed because of its similarity to schizophrenic episodes. Arylcyclohexylamines like PCP are considered to produce one of the best drug-induced models of schizophrenia (Luby et al. 1962; Itil et al. 1967). These clinical manifestations are even more frightening when misinterpreted by the public. In addition, chronic PCP use in some individuals can produce a long-lasting schizophrenic episode, which in some cases may not be reversible. These effects can be produced in humans at doses ranging from 5 milligrams (mg) to greater than 10 mg. Consequently, treatment for PCP abuse is needed and, in fact, may be most necessary to offset the behavioral toxicity that occurs at only moderate doses.

The pharmacological effects of PCP and related arylcyclohexylamines are produced through interaction with several neurotransmitter systems, ion channels, and catecholamine uptake systems. These sites include the so-called PCP receptor that is associated with the N-methyl-D-aspartate (NMDA) receptor complex (Lodge et al. 1983; Vincent et al. 1979; Zukin and Zukin 1979) and the dopamine reuptake site that may also significantly contribute to PCP abuse and psychosis (Chaudieu et al. 1989; Vignon et al. 1988).

NMDA receptor antagonists such as PCP can be protective against brain damage in neurological disorders such as stroke (Olney et al. 1989; Rothman 1984), but can also cause dose-dependent morphological damage to neurons in the cerebral cortex of rats (Olney et al. 1991). Although these effects appear to be reversible after a single dose, effects after chronic doses have not been studied and it is conceivable that chronic use of the drug could be associated with more permanent neurological damage. In addition, female rats are twice as sensitive to these effects as male rats (Olney et al. 1989). This increased potency of the drug in female rats is also found with other pharmacological effects of PCP. The mechanisms underlying these sex differences in the pharmacological effects in rats are poorly understood, but they are dose dependent and are found after single and chronic doses of the drug (Olney et al. 1989; Wessinger 1995). In addition, females are much less efficient at metabolizing PCP than males. Although sex differences of this type are not found in humans, this sexual dimorphism in the rat could be a useful model for mimicking the wide range of differences in effects and metabolism of the drug in humans.

IMMUNOTHERAPY FOR TREATMENT OF DRUG OVERDOSE

Treatment of the adverse effects of PCP is difficult for several reasons. PCP has a very high volume of distribution (6.2 liters per kilogram (L/kg) in humans) and its clearance is primarily by metabolism (Cook et al. 1982) with only a small contribution from renal excretion. Its major sites of action in the central nervous system (CNS) are far removed from the beneficial effects of most traditional treatment methods such as dialysis. In addition, there is no specific antagonist for PCP's adverse effects. These pharmacokinetic and receptor-medicated characteristics make it very difficult to develop effective treatment strategies. Some of the current methods for treatment of overdose are urine acidification, diazepam administration to control convulsions (Aronow and Done 1978;

Peterson and Stillman 1978), and simply waiting for the patient to get better. Nevertheless, Mayersohn (1985) predicts that even under ideal conditions, urine acidification would only increase systemic clearance (Cls) by about 28 percent and would only decrease the half-life (t_) by about 23 percent (t_ in humans averages about 17 hrs, but can range from 7 to 58 hrs; Cook et al. 1985). This small change in kinetic parameters is not surprising due to PCP's very high volume of distribution and low renal clearance (Mayersohn 1985). Consequently, treatments that can only reduce the amount of drug in the bloodstream will not be effective.

One approach to treating drug overdose resulting from CNS-acting, high- distribution volume drugs is the use of high-affinity, drug-specific antibodies (Colburn 1980; Owens and Mayersohn 1986; Smith et al. 1979). Currently, the only drug toxicity routinely treated by immunotherapy is the cardiac toxicity due to digitalis (Smith et al. 1982). The use of anti-drug antibodies for treating toxicity due to CNS-acting agents like PCP is currently being tested in a rat model (McClurkan et al. 1993; Valentine et al. 1994). These studies show that the anti-PCP Fab can dramatically change PCP pharmacokinetics (table 1).

Earlier pharmacokinetic studies with a tracer dose of [^{3}H]PCP (4 micrograms (g)) and very low doses of goat anti-PCP Fab (0.5 to 1 mg) in dogs suggested the therapy could be beneficial (Owens and Mayersohn 1986). However, the major limitation at the time of these earlier studies was the inability to produce large quantities of drug-specific antibody. The development of large-scale techniques for the production of monoclonal antibodies of desired specificity has made immunotherapy a more attractive possibility for treating toxicity associated with drugs of abuse. These large-scale techniques for monoclonal antibody production include ascites production and hollow fiber bioreactors. Hollow fiber bioreactor techniques for large-scale production of a high-affinity murine monoclonal antibody are capable of producing gram quantities of monoclonal antibodies on a daily basis for extended periods of time. This technique is the preferred method since it does not require the use of live animals, and the production scale can be significantly increased over other methods. These are essential features since treatment of PCP overdose in humans will probably require several grams of Fab.

TABLE 1. *Comparison of the pharmacokinetics of PCP, anti-PCP Fab, and PCP after treatment with anti-PCP Fab in Sprague-Dawley rats.*

Pharmacokinetic parameter	Anti-PCP Fab[a]	PCP[b]	PCP after treatment with anti-PCP Fab[b]
Vss*	0.55 L/kg	12.6 L/kg	0.6 L/kg
Cls	2.7 mL/min/kg	66.3 mL/min/kg	6.8 mL/min/kg
t_	7.5 hrs	3.9 hrs	4.9 hrs

KEY: * = Vss = volume of distribution at steady state.

SOURCES: a = data from McClurkan et al. 1993; b = data from Valentine et al. 1994.

From a pharmacokinetic standpoint, the potential for this new class of biologically based drugs (designer antibodies) is very exciting. Antibodies would be expected to have a totally different set of disposition parameters (volume of distribution, clearance, metabolism, and t_) from the drugs against which they are used as antagonists. Table 1 shows a comparison of the pharmacokinetic parameters for monoclonal anti-PCP Fab, PCP, and PCP after administration of anti-PCP Fab. In addition, the antigenicity can be significantly decreased or completely eliminated simply by digesting the immunoglobulin G (IgG) with papain and removing the antigenic Fc (crystalline fragment) portion by chromatographic procedures (Porter 1959; Smith et al. 1979). This yields two Fab fragments (antigen-binding fragments) each with the same affinity as the parent IgG (figure 1). The Fab fragments also have a ninefold greater apparent volume of distribution compared to intact IgG (Smith et al. 1979). Furthermore, the use of monoclonal antibodies allows greater refinement of both antibody specificity and affinity as well as the possibility for the production of large quantities of a homogeneous protein. When the therapeutic use of human monoclonal antibodies becomes more practical, the potential for protein antigenicity should be reduced even further when used in humans.

From a basic science point of view, it is very interesting to study the effects of a high-affinity antibody on the disposition of a drug such as PCP. This is because PCP has some unique characteristics in terms of its metabolism and pharmacokinetics. First, in the rat and other animal

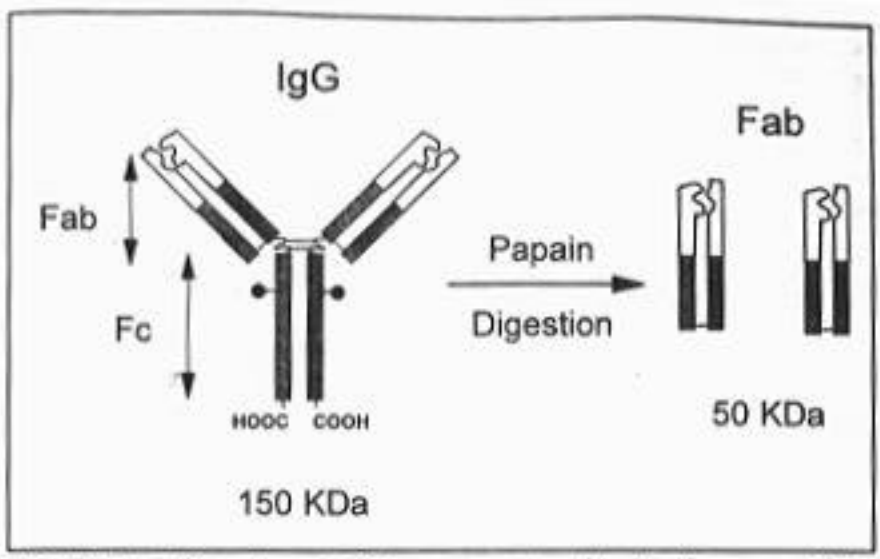

FIGURE 1. *Digestion of IgG into two antigen-binding fragments (Fab) with papain.*

species including humans, PCP has an extremely high volume of distribution (12.6 L/kg in the rat (table 1; Valentine et al. 1994); 6.2 L/kg in man (Cook et al. 1982; see Owens et al. 1987 for a review of PCP pharmacokinetics across species). In contrast, monoclonal anti-PCP Fab appears to have a much smaller volume of distribution (0.55 L/kg or about twice the value of extracellular fluid volume (table 1) (Valentine et al. 1994)). Second, the systemic clearance of PCP in the male rat is over 95 percent due to metabolism, with renal clearance composing only about 1 to 5 percent of total body clearance (Valentine et al. 1994). For comparison, the renal clearance of Fab in the rat comprises about 17 percent of total body clearance. Also, the kidney is an important site for metabolism of Fab (Arend and Silverblatt 1975; Wochner et al. 1967). Consequently, it is essential to determine how the high-affinity monoclonal Fab changes PCP effects and disposition at toxic doses of PCP (Valentine et al. 1994).

A possible drawback to the use of antibodies for the treatment of toxicity is the possibility of anti-idiotypes being produced against the monoclonal antibody binding site. These antibodies could potentially mimic drug-like structural features necessary for binding to a receptor. However, antibodies do not cross the blood-brain barrier in significant amounts and studies to date have not found this to be a problem, especially when Fab fragments are used.

With careful consideration for hapten design, anti-drug antibodies can be used in the treatment of toxicity due to other structurally related compounds. These compounds are usually Schedule I drugs because of their potential for abuse (e.g., 1-[1-(2-thienyl) cyclohexyl] piperdine (TCP) and N-ethyl-1-phencyclohexylamine (PCE). If these other drugs were to suddenly become available to drug abusers, as have a wide variety of fentanyl- and amphetamine-like derivatives, the medical community would not be prepared to treat the toxic effects of these other arylcyclohexylamines. Therefore, it would be most prudent if strategies could be developed for the treatment of a whole class of drugs rather than individual drugs. Indeed, several arylcyclohexylamines appear to have similar effects to PCP, except that they are even more potent. TCP and PCE are about 1.3 to 6 times more potent (respectively) than PCP in drug discrimination assays (Shannon 1981, 1983) and PCP receptor binding assays (see Owens et al. 1988 for a review).

After careful consideration for the structure-activity relationship of arylcyclohexylamines, monoclonal antibodies against a PCP-like hapten (5-[N-(1'-phenylcyclohexyl)amino]pentanoic acid) were generated (McClurkan et al. 1993). These antibodies bind to PCP, TCP, and PCE with a greater affinity than the binding of these ligands to the PCP receptor (Owens, unpublished observation). The development of antibody-based approaches for treating drug classes, rather than just one specific drug, is an exciting possibility and could provide a prototypic model for designing immunotherapeutic approaches for other classes of drugs of abuse.

CATALYTIC ANTIBODIES FOR TREATMENT OF DRUG ABUSE

Another experimental approach for the treatment of drug abuse is the use of catalytic antibodies. The idea behind this treatment is to create an artificial, antibody-based enzyme that can convert the parent drug to an inactive metabolite. This catalytic antibody would then be administered in medical emergencies for overdose or perhaps administered on a chronic basis to persons trying to withdraw from addiction to the drug. In the field of drug abuse, the possibility of using cocaine catalytic antibodies as a therapeutic aid to the treatment of toxicity and addiction has generated the most clinical interest.

Cocaine is a good prototypic ligand to study for this purpose because the drug is naturally metabolized by in vivo estearases, and catalytic monoclonal antibodies with esterase activity are among the few

metabolic reactions that have been successfully mimicked. Landry and colleagues (1993) have generated a monoclonal antibody that can metabolize cocaine to ecgonine methyl ester and benzoic acid. While this approach may have some theoretical advantages over the use of high-affinity anti-drug antibodies, it also has some serious and perhaps insurmountable disadvantages.

The major theoretical advantage to catalytic antibodies for therapy is that, unlike most anti-drug antibodies, they release the breakdown product (metabolite) and are ready to metabolize more drug. Since they continuously regenerate their capacity (like a natural enzyme), they could reduce the body burden of drug with perhaps lower molar ratios of antibody to drug than would be needed for an anti-cocaine antibody. It has been suggested that they could even be used for passive immunization of cocaine addicts during periods of psychological and social rehabilitation to help prevent or blunt drug effects if the patient self-administered cocaine. While these suggested uses could be important from a pharmacokinetic, pharmacodynamic, and immunological point of view, these uses may prove difficult to achieve.

The use of catalytic antibodies for acute toxicity in humans would most likely be only marginally helpful. It is difficult to conceive that this medical approach would have significant advantages over high-affinity anti-cocaine antibodies such as those currently in use for treating digoxin toxicity. It is true that catalytic antibodies could potentially regenerate their capacity after enzymatic turnover of cocaine, theoretically allowing a higher overall capacity for the antibody antagonist. However, in terms of therapeutic effect, rapid reduction of tissue concentrations may be the critical factor in saving lives.

Sudden death is a major factor in cocaine-related fatalities. The mechanism for the cardiotoxicity is not fully understood, but it appears to be poorly predicted from patient to patient. Nevertheless, a rapid immuno-therapeutic response would be essential in treating cocaine-related toxicity, and even catalytic antibodies with low micromolar (M) Michaelis-Menton constant (K_m) values may not be fast-acting enough. By comparison, high-affinity anti-drug antibodies typically have dissociation constant (K_d) values in the low nanomolar (nM) to high picomolar (pM) range. Therefore, to test the usefulness of catalytic antibodies, it will be important to conduct full dose-response curves with the cocaine catalytic antibodies and to

compare these results with the therapeutic effects of similar doses of high-affinity anti-cocaine antibodies as the control.

Currently the immunotherapy literature is not clear about the dose of antibody that would be needed to rapidly reduce the body burden, and thereby the toxicity, of drugs. Nevertheless, some studies suggest it is necessary to use approximately 0.3 to > 1.0 mole equivalent doses of anti-drug antibodies. Since the K_m values for cocaine catalytic antibodies are likely to be relatively high compared to the K_d values for anti-drug antibodies, it is especially difficult to estimate the amount of catalytic antibodies that would be necessary to be effective in various medical situations. Nevertheless, based on the expected high K_m values for cocaine metabolism, the amount of antibody needed for effective treatment will likely be significantly greater than the 0.3 to 1.0 mole equivalents of a high-affinity (low K_d value) anti-cocaine antibody.

Therefore, the greater potential capacity for enzymatic inactivation by catalytic antibodies might be more than offset by their lower effective affinities (i.e., higher K_m values). The higher K_m values would result in very slow metabolic inactivation. The metabolic capacity of endogenous enzyme systems that metabolize cocaine are very high and very efficient relative to the currently available catalytic antibodies. In addition, high- affinity anti-cocaine antibodies are easier to produce than cocaine catalytic antibodies. Since the terminal elimination t_ of cocaine is less than 2 hours (Cook et al. 1985) and the terminal elimination t_ for Fab fragments and IgG are on the order of several hours to a day or more, the normal in vivo metabolic pathways for cocaine could also serve to metabolize unbound drug and thereby regenerate these cocaine-specific antibodies. This would assume that the high-affinity anti-cocaine antibodies would not significantly cross-react with cocaine metabolites.

As another minor point, the use of catalytic antibodies with esterase activity could theoretically lead to autoimmunity against endogenous enzymes. This problem could be partially overcome if Fab fragments were used, or perhaps completely overcome if humanized antibodies or their fragments were used. Also, it is not currently known if endogenous ligands will be substrates for these catalytic enzymes; this could potentially decrease the effective rate for cocaine metabolism or lead to other medical problems.

It has also been suggested that cocaine catalytic antibodies could be used for chronic treatment (for months) of cocaine addicts to augment behavioral modification therapy while patients are withdrawing from the drug. The theory is that if high doses of cocaine catalytic antibodies were present in a recovering addict who then used cocaine, the drug would be efficiently removed or the effects would at least be blunted by the catalytic antibodies. Although this treatment would presumably prevent addicts from adding to their dependence on the drug, it could possibly lead to a dangerous clinical situation. It is difficult to imagine that enough cocaine catalytic antibody could be continuously admini-stered to blunt the effects of cocaine, since enterprising patients would simply take increasing amounts of drug until they obtained the desired effect. In addition, the presence of cocaine catalytic antibodies could actually be a problem because the patient's attempts to titrate effects would be very unpredictable. For instance, if the patient surmounted the effects of the catalytic antibody by self-administering high doses soon after immunotherapy, this dose of cocaine would be too high even a day later when the concentration of the catalytic antibodies had significantly deceased. This could lead to an unexpected overdose.

For now, the major strength in the use of catalytic antibodies is the basic science underlying generation of this unique pharmacological tool. However, it is proving extremely challenging to develop a catalytic antibody with a turnover rate that even approaches the turnover rates of natural cocaine-metabolizing enzymes such as butyrylcholinesterase. Therefore, researchers should first determine if similar approaches, which are currently more technically feasible, might serve the same purpose. For instance, butyrylcholinesterase purified from human blood or high- affinity monoclonal antibodies might be more useful. Nevertheless, basic research on cocaine catalytic antibodies should be pursued since the development of pharmacokinetic and metabolic modifiers of abused drugs is an underexplored area of medications development.

ANIMAL MODELS FOR TESTING IMMUNOTHERAPY

As discussed earlier, high-affinity anti-drug antibodies produce effects on the pharmacokinetics and pharmacodynamics of drugs in animals and humans. For new therapeutic applications, these effects need to be fully tested in animals before administration to humans. In addition, from a basic science viewpoint, it will be necessary to develop relevant pharmacokinetic and pharmacodynamic models of

the effects of immunotherapy on drug abuse. Examples of the scientific questions that need to be addressed are as follows.

The relationships between antibody dose, antibody affinity (or catalytic antibody K_m), and their effects on the drug's pharmacokinetics and pharmacodynamics are poorly understood. For instance, if the drug effect compartment is associated with the pharmacokinetic peripheral compartment, the time needed to reverse drug effects with antibodies would be predicted to be slower than if the effect compartment is associated with the pharmacokinetic central compartment. In addition, it appears that high-affinity antibodies block the metabolism and/or change the metabolic profile of drugs (Owens and Mayersohn 1986; Valentine et al. 1994). These are complex changes that need to be studied in detail, and pharmacokinetic and pharmacodynamic models of these effects need to be developed in animal models before use in humans.

One way to model the genetic polymorphism of metabolism and drug effects in humans is to use the genetic diversity in different strains and sexes of animals such as rats. Although there are not significant sex-related differences in metabolism in humans, sex-related differences in rat liver function have been identified in the last few decades (see Zaphiropoulos et al. 1989 for a review). For example, sexual dimorphism in metabolism with cytochrome P-450 (CYP) rat isozymes occurs with CYP2C13, CYP2C11, CYP2C12, CYP3A2, CYP2A2, and CYP2E1 (Zaphiropoulos et al. 1989). In particular, there are major differences in either the amounts or the expression of the CYP family of enzymes. These enzymes catalyze the oxidation of many steroids, xenobiotics, and drugs (Waxman et al. 1985). These sexual differences are most extensively characterized in rats; in general, the CYP-catalyzed reactions are more efficient in male rats than in female rats. Studying these differences in the pharmacological response resulting from sex-related differences in rat metabolism should provide a useful model for predicting differences in the pharmacological response resulting from genetic polymorphism in human metabolism.

Although these sex-related differences in metabolism have been known for a long time, there is very little data available concerning the role of gender in the metabolism and pharmacokinetics of drugs of abuse. For some drugs of abuse, sexual dimorphism could have important implications and adverse consequences. For PCP, a subject of this discussion, metabolism is the major mechanism for inactivation of pharmacological effects (Mayersohn 1985). In

normal rats, recent data implicate the constitutive CYP2D1 and CYP2C11 isozymes in the formation of PCP metabolites (Hiratsuka et al. 1995; Shelnutt et al., in press).

CONCLUSIONS

Immunotherapy for treating drug abuse appears to be a viable therapeutic approach. To make this experimental treatment a reality, some major hurdles must be overcome. These include the production and purification of very large quantities of antibody at a reasonable cost and increasing the safety of using antibodies in humans. Increased production is currently possible through the use of bioreactors for large-scale production of monoclonal antibodies. Nevertheless, the cost of the antibody is still too high for the day-to-day use in most emergency rooms and clinics. As the technology improves, the cost should be dramatically reduced. To make antibodies safer for use in humans it should be possible to engineer human monoclonal antibodies or to make very small, high-affinity binding proteins based on the knowledge gained from antibody binding site templates.

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