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Evaluation of the anticocaine monoclonal antibody GNC92H2 as an immunotherapy for cocaine overdose

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Abstract

The illicit use of cocaine continues in epidemic proportions and treatment for cocaine overdose remains elusive. Current protein-based technology offers a new therapeutic venue by which antibodies bind the drug in the blood stream, inactivating its toxic effects. The therapeutic potential of the anticocaine antibody GNC92H2 was examined using a model of cocaine overdose. Swiss albino mice prepared with intrajugular catheters were tested in photocell cages after administration of 93 mg/kg (LD_{50}) of cocaine and GNC92H2 infusions ranging from 30 to 190 mg/kg. GNC92H2 was delivered 30 min before, concomitantly or 3 min after cocaine treatment. Significant blockade of cocaine toxicity was observed with the higher dose of GNC92H2 (190 mg/kg), where premorbid behaviors were reduced up to 40%, seizures up to 77% and death by 72%. Importantly, GNC92H2 prevented death even post-cocaine injection. The results support the important potential of GNC92H2 as a therapeutic tool against cocaine overdose.

Keywords: Cocaine-induced toxicity; Monoclonal antibody; GNC92H2; Mice; Immunotherapy

1. Introduction

Cocaine abuse is a serious public health problem with an estimated 1.7 million regular cocaine users in the United States (NIDA, 1996). Associated with the abuse of this drug, 150,000 cocaine-related emergency room incidents were reported in 1995, accounting for 27% of all drug-related emergency room episodes (SAMHSA, 1996). The ingestion of this drug, especially in the form of crack, has increasingly been associated with toxic consequences such as seizures and death. Cocaine-induced seizures are particularly serious aspect of the toxicity associated with this drug. It has been estimated that up to 8.4% (Dhuna et al., 1991) or 12% of patients (Derlet and Albertson, 1989) admitted to emergency departments with cocaine intoxication have seizures among several other health complications. Many studies have now documented these serious toxic effects of cocaine in humans (Bates, 1988; Cregler and Mark, 1985; Mittleman and Wetli, 1984; Gradman, 1988; Garber and Flaherty, 1987; Loper, 1989) and in animal models (Eidelberg et al., 1953; Wilson and Holbrook, 1981; Catravas and Waters, 1981; Bozarth and Wise, 1985; George, 1991). Although vascular, respiratory, thermoregulatory and cardiac dysfunctions are frequently associated with cocaine overdose, the physiological and biochemical sequelae after administration of large amounts of cocaine that result in death have been related to the central nervous system (CNS) (Ritz and George, 1993). Although the effects of cocaine on peripheral cardiac adrenergic receptors are well known and appear to be mediated by noradrenergic and cholinergic neurotransmitter systems (Rappolt et al., 1977; Benowitz et al., 1979; Langer and Enero, 1974; Sharkey et al., 1988), it is also possible that CNS receptors may in part mediate cocaine-induced cardiac dysfunction.

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Cocaine produces its toxic effects and a variety of other physiological and behavioral effects through its interactions with several distinct CNS receptor sites. It is well established that cocaine inhibits neuronal uptake of dopamine, norepinephrine and serotonin, and that the transporters for these neurotransmitters appear to be labeled by [^{3}H] cocaine (Reith et al., 1983; Kennedy and Hanbauer, 1983; Calligaro and Eldefrawi, 1987). In addition, receptor-binding studies have shown that (−) cocaine interacts with both *sigma* and muscarinic cholinergic receptors in the brain (Sharkey et al., 1988). Furthermore, lethal responses to cocaine might also be associated with the convulsant properties of this drug, whereby death might result from tonic respiratory paralysis. Convulsions associated with cocaine use have been reported for over a century, and the reported incidence of seizures associated with ingestion of large doses of cocaine has increased significantly over the past several decades (Coy-Kwong and Lipton, 1989; Myers and Earnest, 1984; Alldredge et al., 1989; Farrar and Kearns, 1989; Jonsson et al., 1983; Lowenstein et al., 1987). However, further work suggests that seizures and lethality are mediated by distinct neuronal mechanisms (George, 1991; O'Dell et al., 2000a,b).

Several strategies have been used in search for optimal medications and treatment regimens for cocaine abuse with very little success. It is clear, however, that overdose must be treated differently from dependence, withdrawal, and relapse, as different mechanisms may be involved in each of these events. Over the last decade, our group and others have reported a large body of work involving the preclinical application of immunopharmacotherapy for the treatment of cocaine abuse (Bagasra et al., 1994; Carrera et al., 1995, 2000, 2001; Fox et al., 1996; Ettinger et al., 1997; Kantak et al., 2000, 2001). With this approach, the unwanted secondary effects of conventional pharmacotherapy are circumvented, as this protein-based technology targets the peripheral sequestration of cocaine, thus impeding its passage into the central nervous system without affecting the organism's natural neurochemistry. The successful implementation of vaccination as a therapeutic means against cocaine abuse, using either inoculation with cocaine–protein conjugates, monoclonal anticocaine antibodies or catalytic cocaine antibodies, will depend on the aspect of the physiological and behavioral characteristics of the health problem in question. In the case of cocaine overdose, it is clear that passive immunization with specific anticocaine antibodies, whereby the dose of cocaine-neutralizing proteins can be controlled, would be the most therapeutically sound strategy. Earlier studies have demonstrated the potential of such strategy using catalytic cocaine antibodies (Mets et al., 1998; Briscoe et al., 2001). Given the nature of the hypothesis at test, a cocaine overdose model was deemed as the only methodological tool that would provide face value to the clinical potential of the proposed immunopharmacotherapy. The use of this animal assay will allow for further investigation avoiding the need to resort to death as an endpoint. Therefore, we now describe the in vivo studies of the anticocaine monoclonal antibody GNC92H2 applied in an animal model of cocaine overdose. We examined the blocking effects of GNC92H2 before and after LD50 cocaine treatment, by measuring cocaine-induced premorbid behaviors, seizures and death.

2. Methods

2.1. Subjects

Male Swiss Webster mice (20–40g) $n=10$ purchased from Taconic Farms at 5 weeks of age were used. Animals were housed four per cage in a 12:12-h light–dark cycle (lights off at 09:00 h). Water and food pellets were continuously available in their living cages. All the experiments described in this study were carried out in accordance with the guide for the care and use of Laboratory Animals as adopted and promulgated by the US National Institutes of Health, and were approved by the Animal Care and Use Committee at the Scripps Research Institute. Every effort was made to reduce the number of animals used.

2.2. Catheter implantation

Mice were placed under general anesthesia with isoflurane vapor mixture and then surgically prepared with a silastic indwelling catheter in the right external jugular as described in detail elsewhere (Ritz and George, 1993). The catheter was made of silastic tubing (id 0.3 mm, od 0.64 mm; 12 mm in length). The jugular catheter was passed subcutaneously to a polyethylene assembly mounted on the back of the animals. This assembly consists of a Plastic Products guide cannula (C313G) which is bent at right angle half-way down the cannula. Silastic tubing is made soft with a short solvent bath (Hemo-De, 1 min). After drying, the cannula/tubing junction was encased in dental cement with a piece of durable mesh secured to the bottom. The mesh serves to anchor the assembly subcutaneously. After shaving the areas for incision, and application of 70% alcohol and proviedone/iodine solution, incisions were made in the mid-scapular region as well as anteromedial to the right forearm above the external right jugular vein. A catheter was passed subcutaneous from the dorsal incision to the ventral incision, and the silastic tubing inserted into the jugular vein, then tied gently with suture thread to the vein. The dorsal incision was closed using either a veterinary adhesive or a suture. Approximately 30 μl of physiological saline was flushed through the catheter and the catheter was then capped with a tygon stopper.

2.3. Cocaine treatment

One week after catheter implantation, animals were treated with (−) cocaine HCl (National Institute on Drug Abuse) 93 mg/kg, i.p., lethal dose 50% (LD_{50}; Hearn et al., 1991) in a volume of 1 ml/kg, or saline alone (control

Table 1
Experimental design showing GNC92H2 dose and treatment time with respect to cocaine LD_{50} 93 mg/kg (.i.p.) injection

GNC92H2 dose (mg/kg)	GNC92H2 treatment time		
	30 min pre-cocaine	With cocaine	3 min post-cocaine
0 (saline)	$n=10$	–	–
30	$n=10$	–	–
90	$n=10$*	$n=10$	
190	–	$n=10$*	$n=10$*

* $p<0.05$, versus control group.

group). Mice were then placed in Plexiglas cages for 30-min observation sessions, during which the latency and occurrence of premorbid behavior and death were rated. The experimental groups received the cocaine LD_{50} injection across antibody dose and/or treatment conditions (Table 1). A control group ($n=10$) receiving the same dose of cocaine but no GNC92H2 was used to assess the toxicity and lethality of the chosen dose by scoring occurrence and latency of premorbid behaviors and time of death within 1 h.

2.4. Passive immunization

GNC92H2 (30, 90, 190 mg/kg; i.v.) was administered at three time points: 30 min pre-cocaine, simultaneously with cocaine injection (time=0), or 3 min post-cocaine. For the 3 min post-cocaine GNC92H2 treatment, a bolus infusion of the antibody was delivered through a 10-in.-long polyethylene tube attached to the catheter on the animals' back, so as to allow the experimenter to deliver the treatment once the animal was placed in the test chamber without disrupting the animal's behavior by affording full ambulatory range. The 3-min time point was chosen on the basis of preliminary, control studies where the average time at which seizures, a death predictor, were observed was 3.4 min. With regards to the dose of antibody used, the experiments of this study were designed in a post hoc fashion. Antibody doses were allotted in a between-subjects design (Table 1). The lower doses of GNC92H2 to suppress the toxic effects of cocaine in the progression of the GNC92H2 treatment time points dictated further use of the dose for the subsequent experiment, as to minimize the number of animals used. Therefore, for the 30 min pre-cocaine condition, only the two lower doses of GNC92H2 were used (30, 90 mg/kg). When both cocaine and the antibody were given simultaneously (time=0), only the two higher doses of the antibody were administered (90, 190 mg/kg). Lastly, in the 3 min post-cocaine experiment, only the highest dose of the antibody was used (190 mg/kg).

2.5. Behavioral observations

After cage-habituation, mice received cocaine 93 mg/kg, i.p. (LD_{50}) in a volume of 1 ml/kg. Immediately after cocaine injection, animals were returned to the Plexiglass chambers for 30-min observation sessions, where they were scored by a "blind" observer for the occurrence and latency of any premorbid behavior including convulsions (loss of righting posture for at least 5 s, clonic movements), Straub tail response, agitation, followed by seizures (tonic), and death. The incidence of these symptoms was rated in two initial 5-min intervals, followed by two 10-min intervals for a total of 30 min. The occurrence of all rated symptoms, with the exception of seizures, was pooled as premorbid behavior as follows: every mouse obtained a score of yes or no, and then the number of mice showing premorbid behaviors were compared between groups against the control group (Table 1). After data pooling, overall percentage of each group was obtained. Therefore, the data herein presented reflect percentage of animals that exhibited premorbid behaviors, seizures and lethality as a function of GNC92H2 dose and time of infusion with respect to cocaine injection.

2.6. Statistical analyses

Premorbid behaviors, seizures and death were assigned an even value of incidence regardless of time of occurrence. The effects of treatment with GNC92H2 at the three different doses and time points were analyzed using the χ^2 distribution ($p<0.05$).

3. Results

Fig. 1 (PRETREATMENT) illustrates the effects of pretreatment (30 min) with the mAb GNC92H2 on cocaine-induced toxicity. Mice treated with the lower dose of the mAb (30 mg/kg) displayed a symptomatic profile virtually indistinct from that of the saline-treated control group, where the expected LD_{50} incidence of cocaine-related behaviors and lethality were observed. All control animals exhibited premorbid behaviors, 68% seizures, and 56% death. Administration of the 90 mg/kg dose of GNC92H resulted in a significant suppression of percent seizures and lethality (Fig. 1, left/center, lower), (seizures: $\chi^2=8.1$, $p<0.05$; lethality: $\chi^2=8.3$, $p<0.05$). There was a modest but statistically insignificant effect by this Ab dose reflected in the pooled premorbid behaviors measure (Fig. 1, PRETREATMENT/top).

Treatment with GNC92H2 concomitant to cocaine injection (time=0) afforded a significantly protective effect in all measures at the higher Ab dose (190 mg/kg) relative to control animals (Fig. 1, CONCOMITANT), (premorbid behaviors: $\chi^2=6.6$, $p<0.03$; seizures: $\chi^2=6.0$ $p<0.01$; lethality: $\chi^2=8.0$, $p<0.05$. The mid-range Ab dose of 90 mg/kg did not result in a blocking effect at this cocaine injection time point.

Fig. 1 (POST-TREAMENT) shows the effects of passive i.v. infusion with GNC92H2 (190 mg/kg) 3 min after cocaine overdosing. Under these conditions, GNC92H2 significantly suppressed premorbid behaviors by over 30% (Fig. 1, POST-TREATMENT, top) ($\chi^2=8.3$, $p<0.05$). Also,

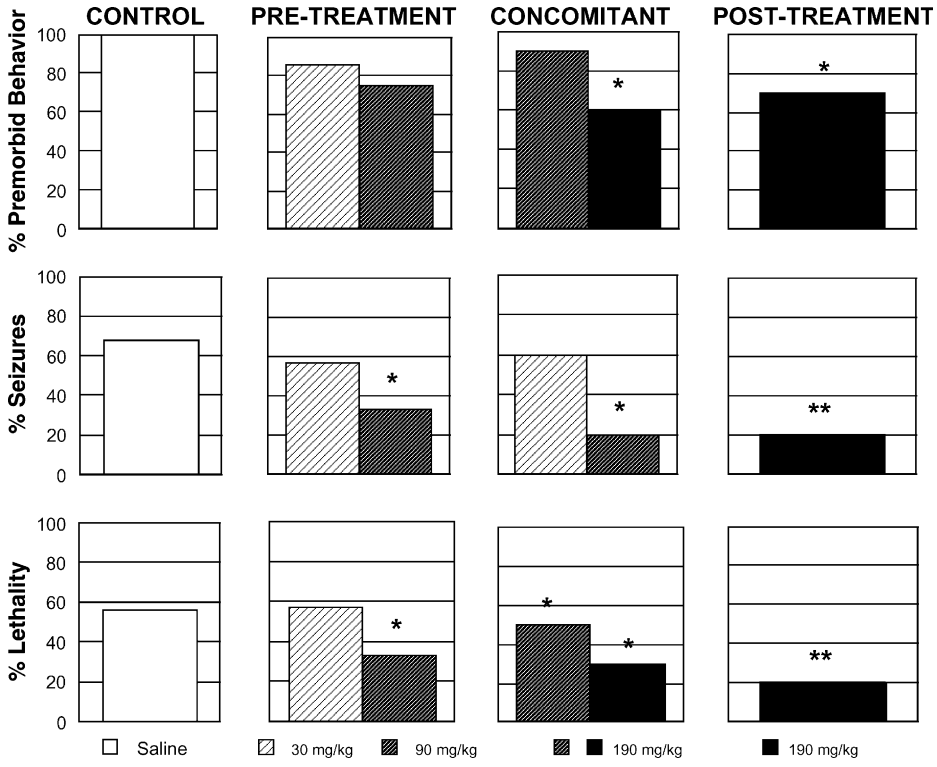

Fig. 1. Percentage of premorbid behaviors (top), seizures (center), and lethality (bottom) induced by cocaine (93 mg/kg; i.p.) 30 min after treatment with GNC92H2 (30, 90 mg/kg) (PRETREATMENT), or concomitant GNC92H2 infusion (90, 190 mg/kg) (CONCOMITANT). In the CONTROL (saline-treated) group, 100% of animals exhibited premorbid behaviors, 68% displayed seizures and 56% expired within 30 min of cocaine injection. GNC92H2 significantly attenuated cocaine-induced toxicity at the 90 mg/kg pretreatment dose (30 min pre-cocaine) at the 190 mg/kg when administered concomitantly with cocaine. POST-TREATMENT reflects the percentage of cocaine-induced premorbid behaviors (top), seizures (center) and lethality (bottom) in animals infused with GNC92H2 (190 mg/kg; iv) 3 min after cocaine injection. Seventy percent of animals receiving the antibody displayed premorbid behaviors, while only 20% where afflicted by seizures or lethality. *($p<0.05$), **($P<0.01$).

seizures and lethality were dramatically blocked by more than seventy percent in Ab-treated animals versus controls (seizures: $\chi^2=6.0$, $p<0.01$; lethality: $\chi^2=5.8$, $p<0.01$).

4. Discussion

The present results provide experimental evidence for the anticonvulsant and antilethal effects of the mAb GNC92H2 in an animal model of cocaine overdose. This study confirms previous reports by this laboratory where the mAb GNC92H2 was found to effectively impede the passage of cocaine into the CNS resulting in a significant suppression of the psychoactive and reinforcing effects of the drug (Carrera et al., 2000, 2001). Furthermore, the protective actions of GNC92H2 were shown to be dose-dependent. Most importantly, this report describes a potential anticocaine therapeutic to offer overdose toxicity protection after cocaine exposure.

The two main variables of the present study were dose of GNC92H2 and time of infusion with respect cocaine injection. Based on the experimental protocol of previous studies, the initial dose and time points implemented were 30 mg/kg (i.v.) of the Ab administered 30 min previous to cocaine injection (i.p.). Although a modest suppressive trend in all behavioral measures was obtained from this dose, the data did not reach statistical significance (Fig. 1 PRETREATMENT). These results were not surprising considering that the amount of peripheral cocaine to be bound by GNC92H2 in the present study was several orders of magnitude larger than that used in the original report (15 mg/kg, i.p.; 0.3 mg/kg/infusion, i.v., versus 93 mg/kg, i.p.). Upon tripling the Ab dose, pretreatment with 90 mg/kg of GNC92H2, resulted in a significant reduction of premorbid behaviors observed (Fig. 1, PRETREATMENT/CONCOMITANT, top), especially wild running and Straub tail (data not shown). These two behaviors were absent in 8 out of 10 animals in the Ab-treated group versus a 100% incidence in the controls. The anticonvulsant and antilethal effects of GNC92H2 at the 90 mg/kg dose were consistently robust as compared to the control and 30 mg/kg group (Fig. 1, PRETREATMENT/CONCOMITANT, center/lower). These results draw an interesting pharmacological parallel to a previous findings where an anticocaine catalytic antibody was tested against cocaine's reinforcing and toxic effects (Mets et al., 1998). In the Mets et al., 1998 study, the catalytic mAb 15A10 was shown to protect rats against LD_{50} cocaine-induced seizures at a dose of 50 mg/kg, whereas 12 mg/kg of the mAb was used to block the reinforcing effects of i.v. cocaine (0.3 mg/kg/infusion). This antibody–cocaine dose range closely parallels the 90 to 30

mg/kg GNC92H2 doses used to antagonize the toxic and reinforcing properties of cocaine in our laboratories. These data demonstrate that pretreatment with GNC92H2 protects against cocaine's central lethal effects, and significantly blocks cocaine-induced premorbid behaviors and seizures.

Post-treatment with GNC92H2 proved to have dramatic anticonvulsant and antilethal effect against cocaine at the 190 mg/kg dose (Fig 1, POST-TREATMENT). Interestingly, there was a relative paucity of inhibition of premorbid behaviors at this dose. This discrepancy may by explained by the different time-pattern of the emergence of these earlier symptoms (wild running, Straub tail, loss of righting response) versus the later presentation of seizures and death (Miller et al., 2000). In fact, the emergence of these early behaviors was observed and recorded before GNC92H2 infusion. These finding suggest that, while post-treatment with GNC92H2 appears to have significant protective effects against seizures and death, it did not seem to reverse or ameliorate already triggered symptoms, and that, unlike incidence of seizures, these premorbid measures do not seem to be predictors of lethality.

Cocaine overdose patients typically are treated in emergency rooms for vascular arrhythmias, convulsions and coma, but due to cocaine's short half-life (20–40 min) symptomatic toxicity manifests early resulting in death (Mittleman and Wetli, 1984). It is therefore evident that the therapeutic value of an agent targeting cocaine overdose toxicity is contingent not only upon its cocaine-blocking properties but, most importantly, the ability to afford this blockade after cocaine exposure. Earlier studies have demonstrated the anticonvulsant properties of catalytic cocaine antibodies against cocaine's toxic effects centrally (Mets et al., 1998) and peripherally (Briscoe, 2001) using a simple overdose model based on pretreatment with antibody, warranting further assessment of the efficacy of this strategy in a post-treatment model of cocaine overdose. The finding that GNC92H2 inhibited cocaine-induced toxicity several minutes after cocaine exposure is of paramount importance, as it leads this line of research in a direction of greater potential clinical relevance.

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