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Active immunoprotection to cocaine

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Thematic update

ABSTRACT

Introduction

The classic pharmacopoeia used to attenuate cocaine dependency has proved a poor therapeutic efficacy. Based on this clinical and therapeutic discouraging panorama since more than a decade various researchers have developed new therapeutic strategies against cocaine addiction. These new experimental strategies are based on the structural design and synthesis of therapeutic vaccine formulations against cocaine addiction.

Objective

To describe the development and evaluation therapeutic of active immunization against cocaine.

Method

A bibliographical search was made using PubMed, using as descriptors the words "Cocaine" and "Vaccine". 155 articles were obtained which were used for these review 46 items.

Results

A preclinical level, active vaccination generates high levels of antibodies capable of recognizing with high specificity to cocaine in the bloodstream, attenuated the behavioral changes induced by different doses of cocaine.

Discussion and conclusion

Preclinical and clinical results have reinforced "proof of concept" active therapeutic vaccination to pharmacological control to cocaine use relapse in humans, but gave guidelines to the postulation and justification of synthesizing new models of anti-cocaine vaccines of human use.

This experimental pharmacological strategy of "immunoprotective" nature has proven effective treatments that significantly reduce the drug-seeking behaviors, both pre-clinical levels in the rodent model as well as in human.

Key words: Addiction, cocaine, active immune-protection, antibodies and pharmacotherapies.

RESUMEN

Introducción

La farmacopea clásica, empleada para atenuar la dependencia a ciertas drogas de abuso ilegal, como la cocaína, ha demostrado una pobre eficacia terapéutica. Basado en este desalentador panorama clínico-terapéutico, desde hace más de una década diversos investigadores han desarrollado nuevas estrategias terapéuticas contra la adicción a la cocaína. Estas nuevas estrategias experimentales están basadas en el diseño y la síntesis de formulaciones estructurales de vacunas terapéuticas contra la adicción a la cocaína.

Objetivo

Realizar una descripción del desarrollo y la validación terapéutica de la inmunización activa contra la cocaína.

Método

Se realizó una búsqueda bibliográfica con el uso del PubMed, usando como descriptores las palabras "Cocaine" y "Vaccine". Se obtuvieron 155 artículos, de los cuales se usaron 46 para esta revisión.

Resultados

A nivel preclínico, la vacunación activa genera altos niveles de anticuerpos capaces de reconocer con alta especificidad a la cocaína dentro del torrente sanguíneo, atenuando las alteraciones conductuales inducidas por diversas dosis de cocaína.

Discusión y conclusión

Los resultados preclínicos y clínicos han reforzado "la prueba de concepto" terapéutica de la vacunación activa para el control farmacológico de la recaída al consumo adictivo de la cocaína en el humano, sin embargo, dieron pauta a la postulación y a la justificación de sintetizar nuevos modelos de uso humano de vacunas anticocaína.

Esta estrategia farmacológica experimental, de naturaleza "inmunoprotectora", ha demostrado ser un tratamiento eficaz al atenuar significativamente las conductas de búsqueda y consumo adictivo a la cocaína, tanto a nivel pre-clínico, en el modelo del roedor, como en el humano.

Palabras clave: Adicciones, cocaína, inmuno-protección activa, anticuerpos, terapia farmacológica.

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INTRODUCTION

Classic pharmacopeia used to alleviate or remove dependency on illegal drugs such as cocaine has shown little therapeutic efficacy in both the short and long term. Against this discouraging clinical-therapeutic backdrop, various researchers have spent more than a decade developing new therapeutic strategies against drug addiction.

These new experimental strategies are based on the design and synthesis of various structural formulations of therapeutic vaccines.[1-4] When these are dosed in active immunization schedules in animal models such as the rodent or the human being, they induce the production of specific serum antibodies, which recognize and bind these substances in the systemic intravascular space. These antibodies have the ability to remove cocaine circulating in the bloodstream once it is taken by the subject; the antibodies are macromolecular (≈150 kD), which do not normally permeate the blood-brain barrier. They thereby form antibody-drug molecules with a high molecular weight which "kidnap" and impede the permeability of cocaine through the blood-brain barrier.[5,6] As such, in this condition of pharmacokinetically altering the cocaine, there is a very significant reduction in the fraction of "free drug" in the plasma which spreads to the extra-cellular space of the cerebral nervous tissue and which would therefore be available for the joining and functional blocking of the dopamine transporter (DAT).[7,8] As a result, there is a reduction observed in the pleasure reinforcing value caused on the nervous system by cocaine, which brings with it a significant decrease in the percentage of relapses in the addictive consumption of this drug.[1,2] Furthermore, its application as a long-term therapy does not produce secondary collateral toxic effects, which are often detected in classic anti-addictive pharmacopeia commonly used against addiction to this psycho-stimulant substance.[4,9,10]

This experimental "immunoprotective"-style pharmacological strategy has been shown to be an effective treatment to significantly reduce and/or inhibit behaviors of addictive seeking and consumption of morphine/heroin,[11-13] nicotine,14 methamphetamines,[15] and cocaine,[1,16-23] both at the pre-clinical level in rodent models[16,21,22,24,25] and in humans.[9,10,26] The case of cocaine in particular is a notable example of the development of studies on clinical phases I-III in humans.[10,26,27]

In 1974, Bonese and collaborators reported immunization with an immunogenic combination formed through chemical synthesis between a bovine serum albumin (BSA)-type carrier-protein and an opiate alkaloid chemically derived from morphine, called morphine-6-hemisuccinil (BSA-M-6-H). Primates (*Macacus Rhesus*) previously trained to self-administer heroin and cocaine and which were immunized with the immunogenic preparation BSA-M-6-H were capable of generating specific anti-morphine/heroin antibodies, and capable of mitigating self-administration of heroin but not cocaine. This demonstrated the immunoprotective specificity of the procedure of active vaccination and of the antagonism of the anti-heroin/morphine antibodies on addictive consumption behaviors of these opiates in the primate[13] ("therapeutic concept test").

Two decades passed before different research groups began developing active immunity models against cocaine in rodents.[17,28]

Initially the molecular design and synthesis was reported of immunogenic combinations against cocaine through covalent combinations of cocaine to carrier-proteins with high molecular mass (≥ 50 kDa) used exclusively for non-human vaccination. This is the case with keyhole limpet hemocyanin protein[1,16-19,21] or BSA,[22] which allowed the synthesis of KLH-cocaine or BSA-cocaine immunogens.[29,30]

Through the use of a KLH-cocaine structural formulation, Bagasra and collaborators managed to generate specific serum anti-cocaine antibodies in rats, not only detecting increases in the titers of specific serum antibodies (0.004-0.019 mg/ml) by re-administration of the immunogen, but also finding that these were capable of reducing the analgesic effects induced by the drug (25 mg/kg, i.p). However, when the dose of cocaine considerably increased, the animals started to show an increase in "reaction time" in the hot plate paradigm; this suggested that the titers of specific antibodies generated by the KLH-cocaine immunogen were not optimum to neutralize the analgesic effects induced by high doses of cocaine.[16]

At the same time, Carrera et al. showed that immunization with a combination of KLH-cocaine (three immunizations with a concentration of 250μg) called GNC-KLH generated high titers of antibodies (1:25000) with a high affinity for cocaine (Kd1mM), which significantly reduced locomotor activity and stereotyped behaviors induced by intra-peritoneal administration of cocaine (15mg/kg), but no more than behaviors generated by the administration of amphetamines.[17,18] Furthermore, the GNC-KLH model managed to significantly reduce - by almost 80% - the tissular levels of "free cocaine" in cerebral tissue (striate and cerebellum) of immunized animals.[17] However, these levels of antibodies were not sufficient to block the re-establishing of behavioral alterations induced upon increasing the dose or frequency of cocaine consumption.[19]

Later, the same working group designed and synthesized a new structural model of immunogenic combination against cocaine called GND-KLH.[18]

This model achieved a dramatic reduction in locomotor sensitivity induced by intra-peritoneal administration of cocaine (15mg/kg). But it did not manage to reduce motor alterations caused by high and serial doses of cocaine (≥ 25 mg/kg, i.p.); this is probably due to the "defeat" of the neutralizing capacity of the maximum titers (≈1:25000) of specific serum antibodies which this vaccine model gen-

erated after the third immunization.[18] However, the GND-KLH model[19] showed a notable improvement with respect to the GNC-KLH model; it blocked the effects of locomotor sensitization induced by cocaine in the longer term, upon generating a humoral immunity, almost two weeks after the last re-immunization.

Other groups developed the design and generation of other vaccine formulations in parallel, with the aim of improving efficacy to stimulate a more robust humoral immunological response with higher concentrations of specific serum antibodies against the drug.[19,21,31,32] For example, using the same system of carrier proteins (KLH) with the covalent chemical union of cocaine, by means of a photo-activatable crosslinker spacer arm (N-hydroxysucciamide-4-azidobenzoate), it was demonstrated that the active vaccination with this immunogenic combination generated a marginal attenuation of the analgesic effects and pleasure reinforcement induced by administering cocaine to the immunized animals.[21,31]

At the same time, Fox et al. demonstrated that three serialized immunizations (10µg/inoculation/animal) with the IP-1010 vaccine, formulated with norcocaine combined with BSA as the carrier protein, was effective in generating maximum concentrations of circulating anti-cocaine antibodies in a range of 0.008-0.070 mg/ml in the immunized animals, two weeks after the third immunization. These titer levels of antibodies were able to induce immunizing effects against the reacquisition of searching behaviors and consumption of cocaine in rats previously trained to self-administer cocaine intravenously (1.0 mg/kg/infusion).

However, only those animals with antibody levels above 0.05 mg/ml (in mice, the titers of antibodies were around 1:100000) and with extreme specificity to rapidly join the cocaine molecules, were able to show a significant reduction in the seeking behaviors and consumption of cocaine.[22,33]

Later, with the aim of increasing the immunizing capacity of the IP-100 vaccine, norcocaine was combined with recombinant cholera toxin b. Immunization against this combination significantly reduced self-administration behaviors in the rat, but only in animals that showed total quantities of serum antibodies higher than 0.05 mg/ml. However, when the infusion of the drug typically produces convulsions and death, in animals immunized with IP-1010, it only produces stereotyped locomotor activity and a low behavior of seeking the drug.[34,35] This suggests an improvement in the specificity of the cocaine antibodies.

With the aim of increasing the concentration and specific circulating antibodies, various research groups developed a new generation of immunodrugs based on genetic engineering, using filamentous bacteriophages as vectors.[36-39]

Janda et al.[20] developed the bacteriophage GNC92H2-p-VIII; of which the surface proteins pVIII were modified, with the aim of generating a type of spongy mesh capable of capturing cocaine molecules within the central nervous system. Twice daily intranasal immunization of rats with the bacteriophage significantly reduced locomotor activity, but only for low to medium doses of cocaine.[36,37,39] These studies concluded that the efficacy of the bacteriophage GNC92H2-p-VIII in capturing cocaine was dependent on the number of copies generated.

Given this limitation, this group decided to utilize the capsid protein of the adenovirus, which is highly immunological in humans, to develop a construct in which a robust immune response could be found through joining the hapten with the capsid protein.[39]

In a first attempt, the first vector was made up of an adenovirus-5 coupled with the first generation of GNC hapten. When administered, this generated high titers of antibodies[38] capable of reducing the stimulating psychomotor effects of cocaine in mice. Furthermore, the titers of antibodies remained at high levels until up to three months after the last administration.[36] This suggests that the adenovirus may be a powerful adjuvant capable of activating the immune system.

With the aim of increasing the immunogenic potential even more, another vector model was developed using the third generation of hapten called GNE, joined to the capsid of an adenovirus-5. This vector was called "dAd5GNE". This new generation of vector generated high titers of antibodies,[37] which managed to remain four months after the last immunization and which were capable of reducing locomotor sensitivity and drug seeking and consumption behavior in animals trained to self-administer cocaine.[37]

Studies in primates showed that the dAd5GNE vaccine did not only limit access of cocaine and its metabolites to the brain (assessed by the evaluation of the union of cocaine with the DAT in the striate) and to peripheral organs susceptible to the harmful effects of cocaine. Histopathological studies demonstrated that organs of animals vaccinated with the dAd5GNE vector did not show adverse effects in the tissue structure of various organs.[40] Furthermore, this study determined that cocaine occupied 62% of the DAT in the caudate nucleus and putamen in non-vaccinated animals. On the other hand, animals vaccinated with the dAd5GNE vector which showed high titers of antibodies showed less than 20% of the DAT occupied by cocaine.[41]

However, one of the disadvantages of the use of the adenoviral vectors is that very often the subjects already have pre-existing anti-adenoviral antibodies. This limits their use. De et al. recently immunized mice with the Ad5 vector, with the aim of generating an immune response to the vector in the animals, and they later immunized them with the dAd5GNE vaccine. The vaccinated animals generated high titers of anti-cocaine antibodies, even in animals previously immunized with the adenovirus.[42] This suggests that the dAd5GNE vaccine is capable of avoiding cocaine's access to

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the brain, even in subjects with an immune response to the adenovirus.

Other groups have used different strategies to optimize the generation of high and specific titers of antibodies through the development of new haptens.

Cai et al. assessed the stability of different haptens (GNNA, GNNS, GNE, and GNC), and found that the hapten most structurally similar to cocaine and which presented a longer average life was one which also generated the highest concentrations of specific IgG against cocaine. It was also the one which gave the best protection against the locomotor activity induced by cocaine.[43] Janda et al. used fluorinated haptens, finding an improvement in the antigenic properties of the vaccine, significantly increasing the affinity of the union and the selectivity of the antibodies.[44,45]

A vaccine has recently been developed against cocaine using analogues of the transition state of cocaine (GNT). The GNE-KLH vaccine (used like hapten to cocaine) generated high levels and persistent titers of specific antibodies against cocaine, which were able to reduce locomotor activity induced by cocaine.[43] Immunization with the GNT-KLH vaccine also generated potent titers of antibodies, but these were catalytic in nature, and were capable of blocking the motor response in mice. However, through repeated administrations of cocaine the protection induced by these antibodies was gradually diminished.[43]

CLINICAL MODELS

Studies in humans are currently up to clinical phase III,[2,4,10,26,46,47] aimed at assessing the variables of immunogenicity, biological safety, and immunoprotection of a structural model of an anti-cocaine vaccine (called TA-CD, Cantab Pharmaceuticals, UK). This structural vaccine model was designed and synthesized using cocaine as hapten, which was covalently bonded by means of a hydrocarbon-type spacer arm to the subunit-B of the cholera toxin and formulated with aluminum.

During the trials in clinical phase I,[2,26] 15 subjects were assessed who were dependent on cocaine, and who were found to be at least three months into the phase of abstinence from consuming the psychostimulant. An assessment was made of the capacity of the TA-CD vaccine to stimulate the production of specific anti-cocaine antibodies (immunogenicity) and possible toxic adverse effects were determined (biological safety), such as fever, allergic reaction, inflammation, edema, tissue damage, adverse immunological effects, nausea, and hypotension, among others, caused by intramuscular dosage of three different doses of the TA-CD vaccine (13, 82, and 709 µg/inoculation) in a sequence of three inoculations. The humoral response was determined 21 days after each revaccination for a total period of 12 months.[26]

The results indicated that this immunization scheme was capable of generating the production of specific anti-cocaine antibodies in a way that was directly proportional to the dosage of the immunogen given (with a specific serum immunoglobulin concentration of ≈3µg/ml). Significant titers were detected after day 42 after the start of the immunization scheme (14 days after the second immunization) and maximum titers at 84 days after the first immunization (third immunization; 13µg-101 ± 60, 86µg-109 ± 62, and 709µg-2655 ± 2223) regardless of the application of additional doses of the immunogen. However, just as with the preclinical trials, all subjects assessed over a year with the different doses of the immunogen showed a progressive decline in the titers of antibodies down to a base level almost nine months after the last immunization. The speed of the decline was inversely proportional to the dosage of the vaccination applied.[26]

The analyses of specificity and affinity showed that the antibodies generated by the TA-CD vaccine did not show cross-reactivity with the primary metabolites of biotransformation of this psychostimulant (benzoylecgonine and ecgonine) and recognized cocaine with high affinity (2.5×10^{-8} M).

In terms of biological safety, the TA-CD vaccine did not show toxicity and lethality in animals, even at doses up to ten times higher than those proposed for humans. No adverse effects related to the administration of the vaccine and the use of the recombinant cholera toxin (rCTB) were observed in humans.[2,9,26]

Once the initial parameters of biosafety and immunogenicity of the TA-CD vaccine were assessed, subsequent studies were carried out in clinical phase IIA with this vaccine model in subjects selected from a population of volunteers dependent on cocaine in the phase of maintaining abstinence and early post-detoxification recovery.[10]

In this study, the experimental groups were exposed to five serialized immunizations of the TA-CD vaccine at doses of 100 and 400µg/inoculation for two months, with the aim of determining the spectrum of immunogenic potency.

The results showed that subjects immunized with a dose of 100µg/inoculation of the TA-CD vaccine reached the maximum titer of anti-cocaine antibodies in circulation after the fifth immunization, whereas subjects exposed to five immunizations at a dose of 400µg of the TA-CD vaccine generated levels of antibodies that were 24 times higher than those detected in the 100µg dose of vaccine after the third immunization.

Even if the statistical analysis resulted in the highest titers of antibodies correlating with periods of lower cocaine consumption in the subjects treated, based on the urinalysis findings of the benzolyecgonine metabolites, the levels of antibodies in the majority of subjects was not significantly higher than those obtained in the first study of phase I[26] of the TA-CD vaccine.

Some 114 outpatient subjects were used for the trials in clinical phase IIb. These subjects were found in an abstinence maintenance program using methadone. The patients were submitted to a program of five immunizations, every two weeks, with the TA-CD vaccine at a dose of 360µg/inoculation.[10] The results of the first trials showed that when the TA-CD vaccine generated a concentration of antibodies with a high affinity greater than 43µg/mL, the patients had fewer urine tests that were positive to cocaine. However, only 38% of the subjects in this study achieved this concentration of antibodies.[10]

Later, another study determined the relationship between various external stimulants (monetary incentives) which increased the subjects' motivation to attend the vaccination sessions regularly and meet with the immunization protocol regularly and reliably, with the aim of ensuring a good immunogenic response.

The results showed that almost 77% of the subjects submitted to a vaccination program with financial incentives completed the immunization program, compared to 45% in those who did not receive the incentive. This suggests that external stimulants such as financial incentives can be a useful tool to increase and/or maintain patient adherence to the vaccination program and as such, an increase may be anticipated in the number of subjects who may respond with high titers of antibodies.[48]

Simultaneously, Haney et al. carried out a randomized study in which ten subjects dependent on cocaine were submitted to a vaccination program with one of two doses different to the TA-CD vaccine (82µg and 369µg/inoculation). They compared the subjective effects of cocaine before and after the vaccination, at the 1st, 3rd, 5th, and 9th week.

The results showed that just as in other trials, the generation of antibodies was very variable. Subjects immunized with a dose of 369µg/inoculation showed high levels of antibodies compared to subjects vaccinated with a dose of 82µg; in both cases, the titer of antibodies rapidly diminished, after which the immunizations were stopped.

In terms of the subjective effects of cocaine, the subjects who showed the highest levels of antibodies (greater than 1:2000) reported the lowest scores in questions referring to "Good Effects of the Drug" and the "Quality of the Cocaine". This suggests that the antibodies impeded the drug passing into the brain and reduced the subjective effect induced by cocaine.[2]

Given that the main difficulty found in the phase I and II clinical trials of the TA-CD vaccine was that only a minority of subjects were able to generate a robust immune response, different studies have been carried out oriented towards determining the reasons for this. For example, it has been suggested that subjects who abuse cocaine could generate antibodies against it.[49,50] Orson et al. assessed the serum of 55 subjects who showed a low immunogenic response and they correlated this with the possible presence of anti-cocaine antibodies.

The results showed that subjects who developed a robust immune response to cocaine (11µg/ml) before TA-CD immunization were not able to generate high titers of antibodies.[50]

On the other hand, the use of the dopamine-β-hydroxylase (DβH) gene and the kappa opioid receptor gene (OPRK1) has been analyzed to identify a subset of individuals for whom active vaccination treatment with the TA-CD combination would be an effective pharmacological treatment for cocaine dependency. In order to do this, 114 subjects dependent on cocaine and opioids were analyzed, who had received five immunizations in the first 12 weeks.

The results indicated that in patients who showed a low level of expression of the DβH and OPRK1 genes, immunization with the TA-CD vaccine generated low titers of antibodies, whereas patients with normal levels of DβH and OPRK1, had high titers of antibodies against cocaine.[47,51]

These results suggest that not all subjects dependent on cocaine are candidates for immunization with the TA-CD vaccine and that good molecular (gen DβH and OPRK1) or biochemical markers (antibodies for cocaine) are required to determine whether or not a patient is a candidate for immunization with the TA-CD vaccine.

However, all of these preclinical and clinical results together reinforce the "the concept test" of therapy for the vaccination and active immunization for the pharmacological control of relapse into addictive consumption of cocaine in humans, but they also give a model for the application and justification of synthesizing new models of anti-cocaine vaccines for human use.[52,53,54,55]

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Conflict of interests

The authors do not declare any conflict of interest.

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