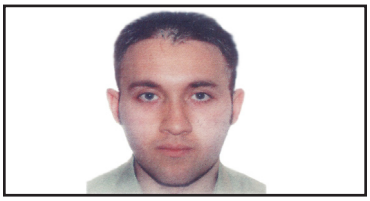
Cocaine Vaccination:
A Novel Approach towards Addiction Therapy



Amjed Kadhim-Saleh

Cocaine addiction has serious social and economic ramifications. Many psychology-based therapies have been utilized to reduce cocaine-dependence. However, no medications have been developed to specifically remedy cocaine addiction. Immunotherapy is a novel approach that might prove effective in reducing cocaine dependence. This therapy is appealing for its specificity in targeting cocaine as well as its revolutionary approach to viewing cocaine addiction as a medical illness.

Cocaine addiction is a problem that has serious social, economic and health-related repercussions. According to the 2005 World Drug Report, approximately 14 million people worldwide use cocaine. The Canadian Addiction Survey revealed that 10.6% of respondents aged 15 and older reported having used cocaine in their lifetime, a significant increase from 3.8% in 1994 (2004; Collin, 2006). Cocaine abuse has been consistently associated with higher crime rates, homelessness and violence (Cruz, 2006). In the United States alone, where 2.5 million individuals are annual cocaine users, crimes associated with drug dependence amount to $67 billion annually (Martell et al, 2009; Rice et al, 1991). Health risks of drug abuse have also been well-established. For instance, 1 in 3 drug-related emergency room visits in the United States are due to cocaine abuse (Martell et al, 2009). The health consequences of cocaine use vary greatly, including severe cardiovascular, respiratory, neurological and gastrointestinal problems (Cocaine Abuse and Addiction, 1999).

Available Therapies for Cocaine Dependence

Drug-counseling and behavioral therapy are considered the most effective interventions for cocaine addiction. In addition to psychological interventions, there are certain medications that have shown clinical efficacy, including GABA agents and agonist replacement therapy (Karila et al, 2008). For example, disulfiram, which is used to treat alcoholism, can be beneficial in individuals who use both cocaine and alcohol because of its inhibitory effect on dopamine metabolism. Among heavy users of cocaine, the GABA-B agonist baclofen is a common treatment. Antidepressants are often used in conjunction with these drugs to mediate the mood changes that arise from cocaine withdrawal (Mechaber, 2009).

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There are numerous limitations to the therapies described above. For instance, systematic reviews detailing pharmacological interventions, such as antidepressants and dopamine antagonists, cannot conclusively support their efficacy in treating cocaine dependence (Soares et al., 2003; Lima et al., 2003). Psychological interventions that encourage compliance and abstinence have been shown to be more effective in treating cocaine dependence (Mechaber, 2009). However, these interventions can be costly, lengthy, and highly unpredictable in terms of their outcome. The U.S. National Institute on Drug Abuse claims that there are no current pharmaceutical medications that specifically treat cocaine dependence (Cocaine Abuse and Addiction, 1999). As a result, other therapeutic strategies need to be developed.

Immunotherapy

Immunotherapy is viewed as a novel remedy for drug addiction. Several immunological approaches to prevent, or at least hinder, the entry of drugs into the brain have been examined. This article focuses on the use of vaccines as an active immunization strategy, which aim to induce an immune response against cocaine. The possibility of using vaccines to combat drug abuse was first demonstrated in 1974, when a vaccine for heroin addiction was shown to be effective in monkeys (Bonese, 1974). More studies were later conducted to examine the efficacy of immunotherapy in treating other drug-related addictions, such as cocaine and nicotine (Pentel, 2004). This article centers on the mechanism of a promising cocaine vaccine that has been tested in a randomized controlled human trial. The vaccine is using a covalently-linked synthetic cocaine derivative, succinylnorcocaine, with cholera toxin B-subunit protein. Cholera toxin, a carrier, is used because it is antigenic (generates antibodies) while cocaine is not antigenic (cocaine users do not make anti-cocaine-specific antibodies). The cocaine-antibody conjugate is then adsorbed onto an adjuvant of aluminum hydroxide (Martell et al., 2009).

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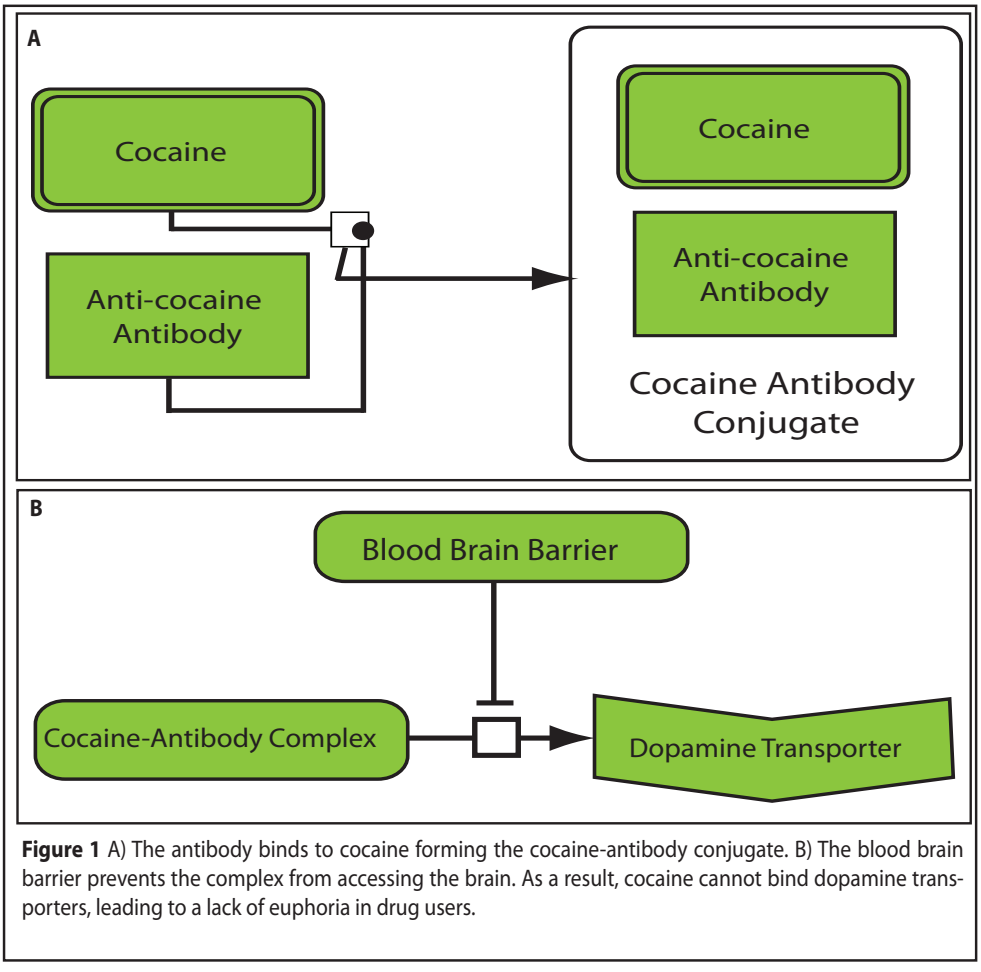

Figure 1 A) The antibody binds to cocaine forming the cocaine-antibody conjugate. B) The blood brain barrier prevents the complex from accessing the brain. As a result, cocaine cannot bind dopamine transporters, leading to a lack of euphoria in drug users.

Mechanism of Action

The cocaine vaccine stimulates the immune system to release antibodies that specifically bind to cocaine, forming Immunoglobulin (Ig) G:drug conjugates that are unable to cross the blood-brain barrier (Figure 1). Since cocaine is prevented from reaching dopamine receptors in the brain, the drug user does not experience the euphoria associated with cocaine use. This is pivotal in reducing the "craving", or drug reinforcement, that often causes relapse in patients who are motivated to quit (Orson et al., 2008).

Increasing Antibody Levels

In order to inhibit cocaine-dependency, a certain level of antibodies must accumulate in the body. This level is calculated using two fundamental values, antibody affinity and the total level of anti-cocaine antibody in circulation (Orson et al., 2008). Antibody affinity is defined as the strength by which an antibody binds to its targeted drug, whereas the total level of antibody in circulation refers to the quantity of IgG. Antibody affinity is calculated using the following equation

$$Ka = [AB]/[A][B]$$

where (Ka) represents the equilibrium constant; (A) and (B) refer to the cocaine drug and anti-cocaine antibody, respectively; and (AB) represents the cocaine-antibody conjugate. The larger the (Ka) value, the stronger the binding (Orson et al,. 2008).

After assessing the affinity of an antibody, it is important to calculate drug concentration in blood circulation. For cocaine, studies have shown that 0.5 μM is present in the blood of addicts (Orson et al, 2008). Figure 2 shows that 20 μg/ml of

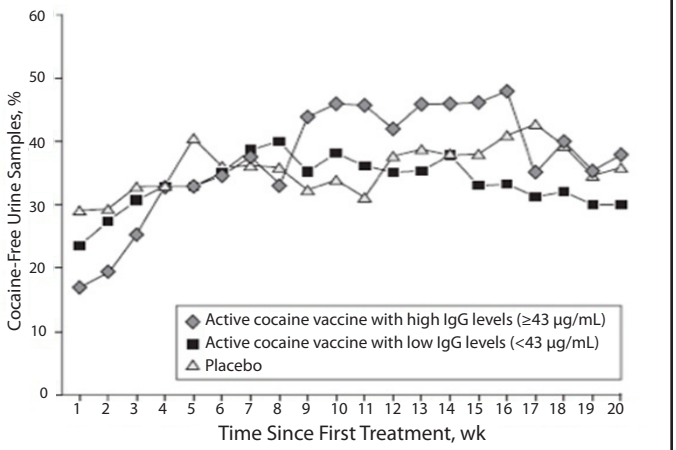

Figure 2 The percentage of cocaine-free urine samples is represented on the Y-axis for the three groups. The X-axis shows the period of experiment in weeks. Values in weeks 9-16 show significant differences between patients with high IgG levels and the other two groups. Values in weeks 1-16 also demonstrate significant differences between groups because patients with high IgG levels had more cocaine-free urine samples than the other two groups. No significant differences were apparent in weeks 17-20 (Martell et al, 2009).

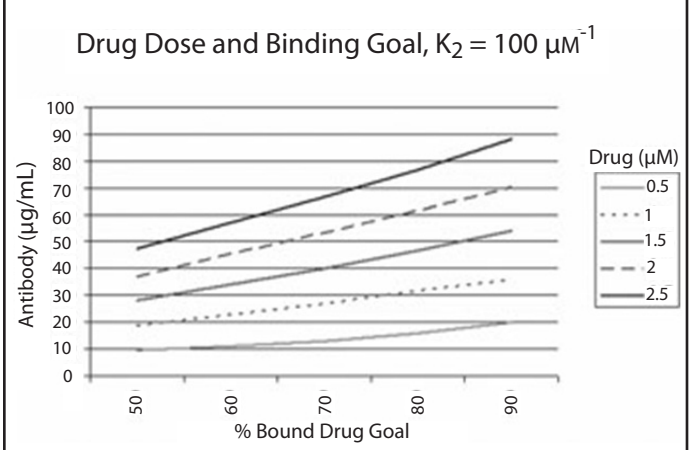

Figure 3 Antibody level and binding goal, assuming an affinity of 100µM−1. The initial drug concentration is given as 0.5, 1, 1.5, 2 and 2.5 µM. The percentage of bound drug is given as a range from 50-90% (X-axis). Target antibody level is graphed on the Y-axis (Orson et al, 2008).

antibodies can theoretically block 90% of a drug at 0.5 µM, given that the antibody affinity is 100 µM−1 as seen in figure 3 (Orson et al., 2008).

Current Results

The use of vaccines in treating cocaine-dependence show limited, yet promising results. In a controlled, double-blind randomized trial, cocaine dependence was reduced in a group of subjects who attained higher than a threshold level of 43 µg/mL cocaine-specific IgG (Martell et al, 2009). Figure 3 provides a comparison between three groups: patients with higher levels of IgG antibodies (43 µg /mL or more), patients with lower levels of IgG antibodies (below 43 µg/mL) and a placebo group.

Patients who attained higher levels of IgG antibodies had significantly reduced levels of cocaine in their urine samples (Martell et al, 2009). Although limited, the success is promising as it indicates that those with higher levels of IgG can become abstinent if motivated to quit cocaine through counseling.

Treatment Benefits

Unlike pharmacological interventions, which do not specifically target cocaine, vaccines induce the production of antibodies which bind to cocaine molecules to prevent them from reaching the brain. Due to this specificity, vaccines are hypothesized to have fewer potential side effects or adverse events (Hatsukami et al, 2005).

In addition to the benefits conferred by the specificity of immunotherapy, this intervention changes how cocaine addiction is viewed. The use of vaccines to treat drug addicts presents cocaine-dependence from a medical perspective rather than an ethical one. Instead of viewing drug addicts as criminals, they are viewed as patients. This shift in understanding may be beneficial in reducing the social and economic implications of drug addiction (Tanner, 2009).

Limitations of Cocaine Vaccines

Immunotherapy alone may not prove effective in eradicating addiction. There has been limited success in sustaining abstinence in drug addicts using these vaccines. For example, in a randomized controlled trial, only 38% of subjects attained a higher level of IgG that are within the target level (Martell et al, 2009). Those subjects had significantly reduced cocaine use. However, those subjects only had a short-term reduction of cocaine-dependency (Martell et al, 2009). According to current guidelines, short-term reduction is insufficient to be considered abstinence (Mechaber, 2009).

Future Direction

Although immunotherapy presents a novel approach to treating cocaine-dependence, its currently limited success necessitates further research. First, better vaccines with effective boosters should be developed to increase the proportion of subjects with antibody levels that fall within the target zone, specifically 43µg/ml. Secondly, these vaccines should produce a longer duration of effect. This increase in antibody levels and sustained duration may lead to a longer inhibition of cocaine-dependency. Finally, the efficacy of vaccines alone is limited; patient compliance and motivation towards abstinence should be encouraged through psychological interventions, such as counseling and cognitive-behavioral therapy, along with immunotherapy.

Postgraduate Editor in Focus

Alba Llop-Guevara is an international student from Barcelona pursuing a PhD degree in the Department of Pathology and Molecular Medicine with a focus in the area of infection and immunity. Seven months pregnant with a baby boy, Llop-Guevara is currently studying the impact of initial immunological disturbances and the role of certain cytokines on the generation of allergic asthma responses in mouse models and house dust mites.

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