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Review

Is immunotherapy an opportunity for effective treatment of drug addiction?

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ABSTRACT

Immunotherapy has a great potential of becoming a new therapeutic strategy in the treatment of addiction to psychoactive drugs. It may be used to treat addiction but also to prevent neurotoxic complications of drug overdose. In preclinical studies two immunological methods have been tested; active immunization, which relies on the administration of vaccines and passive immunization, which relies on the administration of monoclonal antibodies. Until now researchers have succeeded in developing vaccines and/or antibodies against addiction to heroin, cocaine, methamphetamine, nicotine and phencyclidine. Their effectiveness has been confirmed in preclinical studies. At present, clinical studies are being conducted for vaccines against nicotine and cocaine and also anti-methamphetamine monoclonal antibody. These preclinical and clinical studies suggest that immunotherapy may be useful in the treatment of addiction and drug overdose. However, there are a few problems to be solved. One of them is controlling the level of antibodies due to variability between subjects. But even obtaining a suitable antibody titer does not guarantee the effectiveness of the vaccine. Additionally, there is a risk of intentional or unintentional overdose. As vaccines prevent passing of drugs through the blood/brain barrier and thereby prevent their positive reinforcement, some addicted patients may erroneously seek higher doses of psychoactive substances to get "high". Consequently, vaccination should be targeted at persons who have a strong motivation to free themselves from drug dependency. It seems that immunotherapy may be an opportunity for effective treatment of drug addiction if directed to adequate candidates for treatment. For other addicts, immunotherapy may be a very important element supporting psycho- and pharmacotherapy.

Q4 Drug addiction is one of the most serious social and medical pathologies, and the number of people at risk of addiction is still growing. Addiction is typically treated with psychotherapy sometimes combined with pharmacotherapy. The effects of such treatments have not been satisfactory and the search for more effective methods remains a challenge for modern medicine. Immunotherapy is a very promising therapeutic approach. The basic assumption in immunotherapy research is that a vaccine can stimulate the immune system to identify the addictive substances as antigens and produce specific antibodies against them. Binding of specific antibody molecules with a psychoactive substance, prevent them from passing through the blood/brain barrier and thereby prevent their positive reinforcement [1–5]. It seems that a lack of euphoric effect, and hence the severance of the relationship between the intake of the drug and the reward (high), should facilitate the exit from addiction.

The main advantage of this therapy is the lack of adverse effects on the central nervous system, which is often present during pharmacotherapy. The available data from animal and human studies indicate that anti-addiction vaccines present a favorable safety profile [6–8].

Since the molecules of addictive substances are generally too small to stimulate the immune system to produce antibodies, it is necessary to link them with protein carriers. The carriers used for this purpose include, among others, hemocyanin (KLH, *Keyhole Limpet Hemocyanin*), cholera toxin B, tetanus toxoid or recombinant exoprotein A, from *Pseudomonas aeruginosa* [9–11]. The vaccine obtained by combining a psychoactive substance with a suitable carrier produces a plasma antibody–antigen complex too large to pass through the blood/brain barrier and cause their effect [12,13].

There are two methods of immunotherapy: active immunization based on the use of appropriate vaccine and passive immunization based on monoclonal antibodies prepared in a laboratory. In preclinical studies, it was found that both methods of immunization keep the addictive substance out of the brain and thus prevent its action [2,12]. Each of these methods of immunization has some advantages and disadvantages. Since vaccines

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stimulate the immune system to produce antibodies their effect will occur only after a certain period of time. Moreover, usually a single administration of the vaccine does not provide a suitable antibody titer and therefore, it is necessary to provide some boosters [4]. Yet the effect of vaccines lasts longer than the application of monoclonal antibodies. In contrast, the advantage of monoclonal antibodies over vaccines is in the monoclonal antibodies independence of the immune system reaction. The application of monoclonal antibodies, which bind directly to an addictive substance, result in immediate protection. Whereas they quickly block the effect of addictive substances before such substances reach the brain, the duration of the monoclonal antibodies action is much shorter. For that reason antibodies are more suitable for the treatment of symptoms of psychoactive substances overdose, but not for extinguishing addictive behaviors [14–16].

Until now, researchers have been able to develop vaccines and/or antibodies to heroin, cocaine, methamphetamine, nicotine, and phencyclidine. Their effectiveness has been demonstrated in preclinical studies. At present, clinical trials are at different stages of development, in relation to nicotine, cocaine, and methamphetamine.

1. Opioids

Opioids were the first type of addictive substances, for which a vaccine was being sought. Vaccines against morphine and heroin were developed in the early nineteen-seventies and were shown to be immunogenic and capable of binding and retaining morphine in serum [17,18]. It was observed that vaccinated monkeys addicted to heroin, significantly reduced self-administration of this substance [18]. In preclinical studies, it was observed that the vaccines against morphine were effective in reducing behavioral effects of heroin intake both in rodents and primates [18–21].

In 2006, Anton and Leff [22] proposed a bivalent vaccine against morphine and heroin based on the structure of the morphine-6-hemisuccinate (hapten) linked to tetanus toxoid, a highly immunogenic protein as the carrier by a long aliphatic chain containing two stable amide bonds. The vaccinated rats produced a high level of antibodies that recognized both heroin and morphine, sufficient to reduce self-administration of heroin in heroin addicted rats [22].

Next, a vaccine with a novel hapten, 6-glutaryl-morphine attenuated behavioral and psychoactive effects of heroin in rats. This vaccine increased concentration of specific antibodies for morphine and heroin, but not for other opioid compounds, such as buprenorphine, methadone, naloxone, naltrexone, nalorphine or codeine [23]. It is very important because these drugs could be used as a complementary therapy of opioid addiction, or be used as analgesics.

Opioid addicted subjects frequently switch between many different opioids and a vaccine against a single opioid may be only partially effective. For this reason various researchers studied the vaccines' effect against several of the most frequently used opioids and their active metabolites [24]. It turned out that the bivalent vaccine against morphine and oxycodone was capable to produce higher antibody titers against the individual immunogens than in the case of monovalent vaccines.

The latest achievement in the field of vaccines is the development of a "dynamic" vaccine that creates antibodies against heroin and its psychoactive metabolites by presenting multihaptenic structure to the immune system [25]. This vaccine, in heroin dependent rats, effectively prevents heroin reward, drug-induced reinstatement of drug seeking, and reescalation of compulsive heroin self-administration following abstinence. This vaccine is a promising element supporting treatment of heroin addiction.

However, opioid vaccines are not yet in clinical trials.

2. Cocaine

At present, there is no effective therapy for cocaine addiction, therefore immunotherapy may create an opportunity for treating it.

The vaccine consisting of succinyl norcocaine conjugated to cholera toxin B has shown to be effective in blocking the cocaine self-administration. The vaccinated rats showed a high titer of specific antibodies against cocaine, which prevent cocaine from entering the central nervous system [26,27]. This vaccine, initially named IPC-1010 was exclusively licensed to Immu-Logic Pharmaceutical Corp., Waltham, Mass., USA [28]. IPC-1010 was renamed TA-CD when its ownership was transferred to the company Xenova (formerly Cantab) [28]. The first clinical trials were focused on the immunogenicity and safety of the vaccine. The vaccine was well tolerated and there were no serious adverse effects [6,9]. Kosten et al. [6], observed that antibodies appeared after the second injection, their levels depended on the dose and number of injections peaked at three months and declined to baseline by 1 year. The next, an open clinical trial found that despite the cocaine relapse, the person receiving the vaccine did not experience the psychostimulant action of cocaine [9].

Phase II b of clinical trials involved 115 outpatients addicted to opioids and cocaine undergoing substitution therapy with methadone. Levels of antibodies achieved after vaccination differed significantly between clinical trials participants. High levels of IgG ($\geq$43 μg/ml) required to significantly reduce cocaine access to the brain and to prevent its euphoric effect was obtained in only 38% of the vaccinated patients [29]. Because in most subjects the level of IgG was below that considered necessary to discourage the use of cocaine IgM antibodies were also examined. It has been found that detection of IgM antibodies prior to vaccination, which may be the result of repeated use of cocaine, was poor predictor for generating high levels of IgG antibodies in response to the vaccine. Such individuals are inadequate candidates for treatment with the currently available vaccines [30]. In order to find suitable candidates, Kosten et al. [31] carried out a secondary analysis of cocaine dependent patients [29] to find the relationship between polymorphism of the gene for dopamine β-hydroxylase (DBH) and the effectiveness of the vaccine against cocaine. It has been observed that patients with low DBH activity (genotype rs1611115) significantly reduced cocaine intake in comparison to the control group after receiving the active vaccine. In the placebo group, there were no differences neither in the entire group nor in the group with rs1611115 genotype [31]. Authors concluded that the examination of the DBH genotype in cocaine addicted patients could be used to identify individuals for whom the vaccine could be an effective form of therapy.

Phase III of clinical trial did not confirm a significant reduction in cocaine use among vaccinated patients, despite the fact that they had attained the appropriate levels of antibodies [32].

Insufficient immune response in most subjects is still a challenge for new trends in research. As part of this research vaccines based on the specific adenoviral vectors were developed (dAd5GNC, dAd5GNE) [33,34]. These vaccines can induce antibody titers sufficient to eliminate the cocaine-induced psychomotor stimulation in rodents [34]. Moreover, in non-human primates several injections of dAd5GNE induced a high titer of antibodies and reduction of cocaine binding to dopamine transporter (DAT) from 62% to less than 20%. This is far below the threshold of 47% which enables the psychostimulant effect of cocaine [35]. It seems that the vaccines based on adenovirus vectors may be next step toward finding an effective vaccine against cocaine addiction.

Since one of the objectives of using vaccines is protecting patients from exposure to psychoactive substance overdose, Haney et al. [36] investigated their protective efficacy against cocaine in

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