EDITORIAL

When Will the Nicotine Vaccine Be Ready?

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The idea that immunotherapy could be used to treat addictions was first investigated 25 years ago.[1,2] It was shown that specific antibodies against heroin, whether induced by vaccination or administered passively, could alter heroin self-administration in monkeys. Only recently, however, have efforts been made to develop human vaccines to treat nicotine addiction. These vaccines have now entered the clinical phase of development.[3]

Nicotine is the addictive component of cigarettes. The pleasurable effect of nicotine is felt seconds after inhalation of cigarette smoke because of its rapid absorption and delivery to the brain.[4] Therefore, a treatment strategy based on reducing or slowing the distribution of nicotine to the brain might be feasible.

From Animal Models to Human Vaccines

Drug-specific antibodies that bind to drug molecules in extracellular fluid can alter the action of that drug, thus reducing its concentration and distribution to tissues. Antibodies also have the potential to form a reservoir, binding to drug molecules introduced into the organism and thus blocking their effects. Immunotherapy as a way of altering behavioral effects induced by drugs was first studied in monkeys trained to self-administer heroin. Both active immunization (antibody production) and passive immunization (passive infusion of nicotine-specific antibodies) reduced the self-administration of heroin.[1,2] More recently, immunization of rats against cocaine was found to suppress locomotor activity induced by the drug[5] and even self-administration has been shown to be inhibited.[6]

Nicotine has a favorable drug-antibody interaction and immunogens have been reported to induce the appearance of nicotine-specific antibodies in animals.[7] It has been shown that a clinically relevant fraction of nicotine (0.03 mg/kg, equivalent to smoking 2 cigarettes) binds to antibody in serum.[8] The distribution of nicotine to the brains of rats, therefore, is lowered by 38%.[9] Both active and passive immunization modify the pharmacokinetic and pharmacological effects of nicotine, reduce the distribution to the brain, and attenuate cardiovascular response to nicotine and nicotine-stimulated locomotor activity,[10] even when the drug is administered as a continuous infusion.[9] Immunized rats have been reported not to self-administer nicotine,[11] and immunization also suppresses nicotine-induced dopamine release in the nucleus accumbens.[12] Moreover, both types of immunization can actually alleviate abstinence syndrome in nicotine-dependent rats.[13]

Recently, clinical phase I trials have started with 2 nicotine vaccines: TA-NIC, developed by Xenova Research Ltd (Cambridge, United Kingdom),[14] and NicVax™, developed by Nabi Biopharmaceuticals (Rockville, MD, United States of America). The first of these vaccines was tested in a double-blind placebo-controlled trial with 60 healthy volunteers (50 smokers and 10 control subjects) that compared 2 doses and 4 dosing regimens. Preliminary results were presented at the annual meetings of the College on Problems of Drug Dependence (Quebec City, Canada, 2002)[15] and the Society for Research on Nicotine and Tobacco (SRNT) held in Padua, Italy, in 2003.[16] The investigators concluded that the TA-NIC vaccine is immunogenic and safe. The NicVax™ vaccine was presented at the annual European meeting of the SRNT held in Santander, Spain, in 2002[17] and also at the annual meeting of the SRNT in 2003, in Padua, Italy.[18] The vaccine was found to be safe and well tolerated, and to produce sufficient quantities of nicotine antibodies in a double-blind, placebo-controlled trial in 20 healthy subjects. The next step with both vaccines would be to determine whether the antibodies produced can help those with nicotine addiction to stop smoking.[19]

Mechanisms of Action

The nicotine vaccine induces the formation of specific antibodies that bind with high affinity to nicotine in plasma and extracellular fluids, thus preventing nicotine from reaching the brain. There are no side effects. The conjugates formed are too big to

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cross the blood-brain barrier, but antibodies can also lower the rate with which nicotine molecules reach the brain through other mechanisms which are still not entirely understood. To further investigate this, Satoskar et al[20] recently compared rats who were injected single doses of nicotine with another group who were perfused the drug continuously to determine the mechanism by which the vaccine affected the distribution of nicotine to the brain and other organs. Of particular interest was the finding that the effects of the vaccine varied substantially according to tissue. The distribution of nicotine to the brain and—to a lesser extent—to other tissues was lowered at all times, but nicotine levels in body fat and the lungs increased. This would suggest that the vaccine is acting not only by binding to nicotine but also by sequestering nicotine present in serum and redirecting it to other tissues. The formation of antibodies was also more extensive than expected, which would have increased the binding capacity 2 or 3 times.

The release of dopamine in the accumbens nucleus is fundamental in the development of dependence, and the vaccine has been shown to inhibit such release.[12] Passive immunization of rats has also been shown to lower the excitatory effect of nicotine on the locomotor apparatus.[10] The vaccine would evidently reduce the effects of nicotine[21] given that the rats are less able to distinguish between a dose of nicotine and one of saline solution and the symptoms of the abstinence syndrome are alleviated.[13,20,21] This suggests that the vaccine could help prevent relapses by preventing the reinforcing action of nicotine in the brain and the onset of abstinence syndrome.[11] Cerny et al,[22] who evaluated the effect of a nicotine vaccine administered both intranasally and subcutaneously to rats, concluded that the vaccine could break the vicious circle of gratification caused by nicotine in the brain. The authors also found that the protection afforded by intranasal administration is at least as effective as that afforded by subcutaneous administration. The antibodies induced after nasal administration bind less extensively to nicotine in serum than those induced after subcutaneous administration but this would be compensated by greater production of immunoglobulin A in saliva and the respiratory tract. A combination of the two routes of administration would therefore further boost protection. In addition, the authors found that the formation of antibodies was similar regardless of whether nicotine was administered as a single dose or chronically (as would be the case with a smoker) and pointed out that a booster vaccine would be necessary within 2 years of the first dose. As indicated by Sanderson et al,[23] the vaccine is able to generate antibodies that attenuate the behavioral effects of nicotine on the brain, even when the drug is present in high doses. Carrera et al[24] used a rat model of locomotor activity to assess how the vaccine modifies the psychoactive effects of nicotine. The authors found that nicotine-induced psychoactivity in the brain was significantly suppressed in both vaccinated rats and passively immunized ones compared to control animals. The effects of the vaccine might also be due to slower elimination of nicotine because it is less available for hepatic metabolism.[7,25] Such an effect could be beneficial for smokers before they quit smoking entirely. In any case, research teams are actively pursuing more effective vaccines.[26]

Usefulness of the Nicotine Vaccine

From a practical point of view, the vaccine could be useful for preventing relapses,[3,27,28] providing support for smokers to quit by decreasing how often they smoke and eliminating the reward in the brain,[3,9,22-24,29] and for preventing subjects, particularly adolescents, from starting smoking.[3,29] Moreover, the vaccine could help prevent damage to the fetus in pregnant women caused by smoking given that the nicotine-antibody conjugate would not cross the placental barrier. Indeed, the findings of a recent study suggest that the vaccine is useful when used before pregnancy and when the mother is passively immunized during gestation.[30]

Answering Questions

We have seen that current research is slowly managing to answer questions posed about the application of the nicotine vaccine. The vaccine, according to phase I studies, may be useful in humans because it is safe, well tolerated, and induces a rapid increase in antibodies. These antibodies have been shown to act both by binding to nicotine and by sequestering nicotine present in serum and redirecting it to other tissues. More antibodies are formed than expected, further increasing its capacity to bind to nicotine. The protection induced after intranasal administration has been found to be just as effective as that induced after subcutaneous administration and protection is further increased when a combination of the two routes is used. Similar numbers of antibodies are formed regardless of whether nicotine is administered as a single dose or chronically. A booster vaccine is thought to be necessary in humans every 2 years. So, returning to the question in the title, when might a nicotine vaccine be available for humans? Our answer, in view of the studies discussed in this editorial, is 2006.

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