Infecting the brain to stop addiction?

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Drug abuse is a major public health problem, and, although there are many treatments of proven efficacy, the majority of patients are not permanently cured, with relapse rates on the order of 70% or more in the first years for the treatment of almost all drugs of addiction. Therefore, there is a great need for new and improved therapies. Carrera et al. (1) have pioneered the use of one of the oldest proven medical interventions, immunization, in the treatment of cocaine dependence. Their initial studies revealed that it is possible to vaccinate animals against cocaine by using either a blocking antibody (1) or catalytic antibody (2) approach. The blocking antibody binds cocaine and therefore extracts it from the blood; this seems to be the more promising method, because the current catalytic antibodies only minimally accelerate the clearance of cocaine. However, the blocking antibody technique provides only a peripheral blockade, and so any cocaine that is not “mopped up” by antibodies in plasma can enter the brain and give the reinforcing actions that perpetuate the cycle of addiction and dependence. The work by Carrera et al. (3) in a recent issue of PNAS moves the field by utilizing a concept originated for the treatment of Alzheimer’s disease in which an antibody to β-amyloid was delivered to the brain in a (bacterial)phage vector (4). Here, the animal is infected with a phage that targets the brain and that has been engineered to express thousands of copies of the cocaine-binding antibody. It reproduces in the brain, thereby generating large amounts of blocking antibody. When cocaine enters the brain, some of it binds to the antibody and, therefore, is not available to perform its usual action: to increase dopamine, the neurotransmitter that is thought to mediate its actions. To maximize access of phage to the brain and minimize peripheral infection, the phage vaccine was administered intranasally, where it is presumed to enter the olfactory nerve endings and move down the axons into the brain.

**Does Infection Work in Rats?**
The results show that the phage indeed infects the brain of rats and that the antibody is expressed in significant titers. The actions of cocaine were attenuated in parallel, as shown by a reduction in the two major actions of cocaine. These actions are, at low doses, to stimulate locomotor activity and, at higher doses, to induce stereotypy (repetitive behaviors such as rearing and sniffing). The attenuation of both these actions of cocaine show the activity of the antibody is to reduce the effect of cocaine in a manner compatible with pharmacological antagonism (a shift of the dose–response curve to the right). Direct evidence of reduced pharmacological action of cocaine, such as a lessened dopamine increase or reduced self-administration, is not provided in this paper, but is presumably the explanation for the reduction in cocaine-mediated behaviors.

**It is possible to vaccinate animals against cocaine by using a blocking antibody or catalytic antibody approach.**

**Implications for Treatment**
What are the implications for treatment of cocaine or other addictions in humans? For cocaine, this is an exciting new concept in a field that has been characterized by an almost complete lack of effective pharmacological therapies. The concept that blocking the actions of a drug of addiction will lead to reduced use and dependence is well established for opiates, where the antagonist naltrexone has a long track record (5). An antagonist approach to cocaine has been considered by means of drugs that block its access to the dopamine uptake site (6) and block the actions of the dopamine that is released by cocaine to stimulate receptors, e.g., ecopipam (7), although neither approach is yet proven as a treatment. Would there be advantages of the blocking antibody approach compared with that with an antagonist? Because the antibody would be “dormant” except when cocaine was taken, it would appear to be an ideal form of therapy for two main reasons. First, it stops the cocaine effect “at source,” which is easier than blocking the effects of cocaine; because cocaine increases dopamine and several other neurotransmitters, total blockade of cocaine effects would require a series of selective antagonists. Second, in contrast to drug antagonist approaches, the blocking antibody will not affect normal neurotransmitter function. Antagonists of the various neurotransmitters that are responsible for the effects of cocaine would lead to unwanted actions on the many aspects of brain function, for instance, in the case of dopamine, mood, attention, and movement.

**Could the Block Be Overcome?**
However, a critical issue is whether the antibody can provide complete blockade against any dose of cocaine; once cocaine concentrations had risen to saturate the antibody-binding sites, further cocaine would behave as normal. This leads to the concern that users will resort to dose escalation to offset the actions of an antagonist; although this is always a real concern, in practice with naltrexone it seems impossible to overcome the block because the affinity of the antagonist is so much greater than that of the abused agonist (e.g., heroin). However, antibody blockade may be less resistant to increasing dose, and although having to increase the dose to get an effect would be a financial deterrent to cocaine users, undoubtedly some would try to do this. In these cases, there is the real concern that such dose escalation would lead to higher-than-normal peripheral concentrations of cocaine that are likely to be cardiotoxic. There may be ways to circumvent this problem, for instance, by using peripheral as well as brain immunization or by administering catalytic antibodies in brain, because these would not become saturated regardless of the dose of cocaine.

**Will Viruses Work in Humans?**
There are other considerations that need to be considered. Although antagonist therapies are appealing as pharmacological approaches to addiction, they have not proved particularly successful in practice. These therapies are not successful because they are not reinforcing:

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they give no pleasure. Indeed, they may be aversive if they displace residual agonist, such as heroin, from the brain and precipitate withdrawal. For these reasons, drug addicts are generally reluctant to use antagonist treatments unless required to do so by law or as a requirement from a professional body to continue in work. There is no reason to suppose that the antibody vaccination approach will not have similarly low take up. Perhaps an alternative strategy would be to produce an enduring blockade before first exposure as a preventative measure, such as is done with vaccination against measles and other infectious diseases. This would, of course, be ethically controversial, although given the fact that cocaine dependence is more damaging to many individuals than measles, it is an option that should be debated.

In the experiments reported here, the phage was administered on a regular basis several times a day. Moreover, there was a relatively rapid clearance of phage from brain once the period of administration had ended, with levels falling rapidly within a week. This would not be ideal in a human population, where compliance could easily be compromised. However, these are early days for these new molecular technologies, so we can realistically expect significant advances in the methodology in future years. The concept could also be applied to limit the effects of other abused drugs, such as opiates and possibly even cannabis. However, such a blocking approach is unlikely to be effective in the absence of concurrent psychological interventions.