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Quest for Vaccines to Treat Addiction

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ABSTRACT

Drug addiction is a prime example of biochemical psychology. When people use drugs such as nicotine, they trigger dopamine receptors in the brain, causing a pleasurable sensation. People want to repeat the feeling and thus get addicted to the drug. With the development of a vaccine to treat addiction, researchers attempt to prevent drugs from crossing over the blood-brain barrier and triggering the dopamine receptors. Experiments and clinical trials prove the efficacy of the nicotine vaccine. However, Phase III trials and additional research are necessary before the vaccine can be launched for public use.

INTRODUCTION

Addiction is one of the greatest issues facing our society today. Thousands of people struggle with smoking, drugs, and other addictions on a daily basis. What starts as one cigarette or one sip of alcohol often develops into a daily necessity or an ever-present need. However, it is not the cigarette or alcohol that satiates a person; it is the chemical reaction of the dopamine receptors that the addictive substance triggers in the brain that satisfies (Koob and Moal 2001). Addiction is a classic case of biochemical psychology, in which certain activities in the brain cause specific forms of behavior. In this case, the chemical reaction occurring in the brain in response to a drug causes the user to feel a certain reward. This eventually causes one to become dependent on the drug, to the extent that one is willing to forego all ethical limits to obtain more of it. Numerous researchers have attempted to find a way to help addicts recover (Koob and Moal 2001). Previous experiments as well as cutting-edge research have furthered this discovery. Researchers have developed a vaccine to aid in the treatment of nicotine addiction and restore normal brain receptor activities. However, what is the efficacy of the "nicotine vaccine" in treating smokers addicted to nicotine? Before analyzing the effectiveness of the vaccine, a complete understanding of dopamine receptors and their effects on the body and behavior must be gained.

THE BRAIN-BEHAVIOR CONNECTION: DOPAMINE RECEPTORS

Psychologists and scientists have been mystified by the brain-behavior connection in drug or alcohol abuse and have been trying to determine how to treat addiction. Drugs and other addictive substances cause a surge in levels of a brain chemical called dopamine, the neurotransmitter that is responsible for feelings of pleasure. The brain remembers this pleasure and wants to repeat it (Long 2011). Neurons containing the dopamine receptors are clustered in the substantia nigra, an area in the midbrain (Schultz 2010). The pleasure sensation creates the motivation for a person to proactively pursue activities such as eating and drinking that are crucial for survival. A person is driven to perform these vital functions because the brain is conditioned to expect the dopamine rush that accompanies them. Drugs such as methamphetamine, heroin, and cocaine produce their effects by acting on the flow of neurotransmitters and affecting the brain chemistry (Schultz 2010). They can cause profound changes in human behavior (Wise and Rompre 1998) that can have negative consequences in varying areas of an individual's life (Chandler et al. 2009).

Widely documented experimental evidence suggests that the mesolimbic dopamine system is hypofunctional in the addicted brain (Melis et al. 2005). When

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using addictive drugs, the brain is flooded with up to ten times the normal amount of dopamine. The mesolimbic dopamine system becomes hypofunctional due to down-regulation of the dopamine receptor because of excess dopamine present when certain addictive drugs are used. By decreasing the dopamine (DA) system function in addicted subjects, there will be a decreased interest in non-drug related stimuli and increased sensitivity to the drug of choice (Melis et al. 2005). When a user's brain adapts to a higher level of dopamine to get pleasure, it begins associating the addictive drug with this neurochemical reward, and eventually, the drugs create a scenario that only they can meet (Diana 2011). This process leads to addiction, in which a person is left with a drive to compulsively take the drug, conditioned to expect artificially high levels of the neurotransmitter. The brain begins to require more dopamine than it can naturally produce, and it becomes dependent on the addictive drug, which never actually satisfies the need it created (Kosten 2011).

Normally, dopamine conditions us to do what we need to do to continue surviving. Regulation of dopamine plays a crucial role in our mental and physical health. However, just as food is linked to survival in day-to-day living, addictive drugs triggering the release of dopamine begin to take on the same significance for the addict. The need to obtain and take drugs becomes more important than any other need, including truly vital behaviors like eating. Eventually, all ethical guidelines in a person's life, such as family, work, and community obligations and values, are lost to the disease of addiction (Koob and Moal 2001). When the brain's dopamine receptor is down-regulated, greater amounts of dopamine are required to induce the normal effect. Eventually, the disrupted dopamine system renders the addict incapable of feeling any pleasure even from the drugs they seek to feed their addiction. The lack of control causes people who are addicted to continue using drugs, even when the drugs have lost their power to reward (Diana 2011).

Based on the above, one form of treatment used to treat addicted patients is to block entry of the addictive drug into the brain receptor system (Kenny et al. 2006). In this way, the DA system hypofunction will eventually revert to normal functioning with time.

Nicotine Addiction and Treatment

Cigarette smoking is the most common cause of death in industrialized countries. Thirty percent of all deaths in smokers from 35-69 years of age are due to chronic smoking. Though there are many forms of medication available for the addiction, there is still an extremely low success rate for people who have tried to quit smoking. According to the American Lung Association, nearly half of U.S. smokers try to quit each year, and only 4% to 7% of the people who make the attempt are successful. Norman Edelman, the Chief Medical Officer of the American Lung Association, says that at best, only one out of three people trying to quit are successful (American Lung Association 2011).

Therefore, a new approach to treating addiction has been developed. This technique utilizes injected vaccines to block addictive substances from reaching the brain. As indicated in Figure 1, the vaccine induces the immune system to produce antibodies that bind to nicotine. This prevents the nicotine from crossing the blood-brain barrier and acting on dopamine receptors in the brain. When people smoke, the nicotine inhaled from tobacco moves from the lungs to the bloodstream, and up to the smoker's brain within seconds. There, nicotine triggers a number of chemical responses, one of which involves the dopamine receptors, creating feelings of pleasure and a variety of neural effects that initiate and maintain tobacco dependence. The sensation lasts minutes. However, as the nicotine levels drop, smokers feel agitated, a symptom of nicotine withdrawal. In order to relieve discomfort, they often light another cigarette, beginning a vicious cycle of addictive smoking. Therefore, efforts to develop treatment for people addicted to smoking have focused on targeting neural pathways involved in nicotine addiction (Hall 2005).

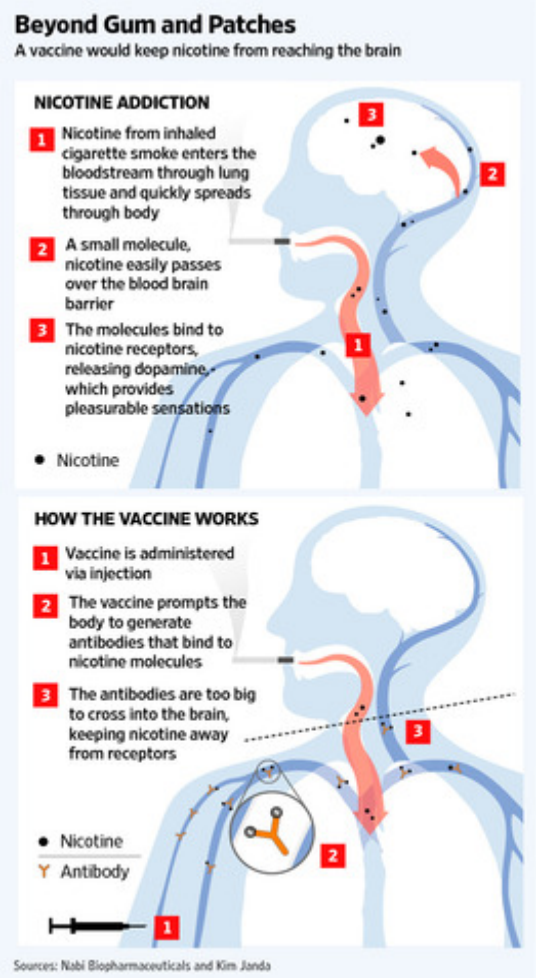

Figure 1: With the administration of the vaccine, the body produces antibodies that bind to nicotine molecules and prevent them from crossing the blood brain barrier. Source: Long 2011

When people take addictive drugs, the drug molecules travel through the bloodstream to the brain. Because addictive drugs are so small, they bypass the immune system completely. However, using the vaccine, scientists attach molecules similar to addictive drugs to much bigger antigens, such as deactivated versions of the common cold virus (Long 2011).

When injected into lab animals and people, these so-called conjugate vaccines spur the immune system to create antibodies to fight the tiny, addictive drug molecules (Kosten 2011). The antibodies attach to molecules of nicotine and cocaine before they cross the blood-brain barrier, thereby blocking them from triggering the pleasure centers in the brain (Hall 2005).

Vaccination against nicotine can reduce the risk of relapse in addicted smokers by easing the pharmacological effects of nicotine for the first few months after quitting, the period when most smokers relapse (Hall 2005). Unlike prior medications that worked via the brain, addictive-treatment vaccines work in the bloodstream (Long 2011).

Vaccines against nicotine are a promising concept in smoking cessation research. This is because it can aid current smokers attempting to quit, former smokers wanting to avoid relapse, and adolescent smokers from becoming confirmed smokers. Because nicotine is the pharmacological agent controlling the rate of cigarette smoking, by reducing the rate and extent of uptake in the brain, researchers can attempt to treat the addiction (Vocci and Chiang 2001). Even if the smoker increases the dosage of nicotine, the rewarding effect would still be circumvented by the vaccine, hopefully ensuring that the lapse would not lead to daily smoking (Khoury et al. 2003). However, the vaccine does not combat cravings. They simply trick the body to reject drugs as if they are foreign pathogens. The vaccine also has the potential to work on many drugs aside from nicotine, such as cocaine and heroin, amongst other addictive substances.

VACCINE FORMATION AND ADMINISTRATION

Since nicotine is extremely small (molecular weight =167 kD) and therefore not immunogenic, the body does not create antibodies against it. By using a linker such as succinic acid, researchers can convert nicotine to an immunogenic carrier protein to form an immunogen, a conjugate nicotine vaccine. Multiple types of carrier proteins have been used, such as keyhole limpet hemocyanine, recombinant cholera toxin B subunit, and recombinant psuedomonas exoprotein A. The latter two have been used in vaccines administered to humans before. The vaccines are then mixed with an adjuvant such as alum, to enhance the immune response (Hieda et al. 1997).

The ideal vaccine elicits antibodies that have the characteristics of immunogenicity, specificity, and affinity to bind to nicotine. Immunogenicity refers to the maximally effective serum concentration of antibody throughout the period of interest. In that way, there will be a higher ratio of antibody to nicotine to increase binding of nicotine to serum. Affinity refers to the strength of the antibodies binding to the nicotine, and specificity refers to the extent that antibodies bind to nicotine as opposed to other compounds (Hall 2005).

EXPERIMENTATION PERFORMED WITH ANIMALS

Studies performed with animals have proven that attaching nicotine to a viable antigenic protein produces antibodies that have a high affinity for nicotine (Hall 2005). A series of 2-4 injections of vaccine was given to rats over 4-8 weeks. The vaccine was aimed at eliciting higher serum concentration of nicotine specific antibodies that would not bind to nicotine metabolites (Pentel and Malin 2002). When the rats were vaccinated, they were given a single dose of nicotine, equivalent to the nicotine absorbed by a smoker from two cigarettes. The researchers then tested the serum and found that the nicotine delivered to the brain 1-3 minutes later was 60% less than that of the control group. Even when the rats received heavier doses, equivalent to that of a chronic smoker, vaccination remained effective in reducing the early distribution of each dose to the brain. Vaccination of rats reduced the nicotine-induced release of dopamine from the nucleus accumbens, a neurochemical event that is thought to be a key mediator of nicotine dependence (Pentel and Malin 2002).

These results indicate that there is potential usage for vaccines in the prevention of relapse. With the effect of the vaccine and the antibodies attacking the nicotine, the nicotine fails to pass through the blood-brain barrier and affect the dopamine receptors. By staying in the blood, there is no pleasurable response to the

nicotine. Cigarette smokers who quit often experience cravings and thus resume smoking to relieve their discomfort. However, if the vaccine renders the cigarette ineffective, the smokers will be less likely to smoke a cigarette. A downside of the experiment was that it only managed to prevent 60% of the nicotine from reaching the receptors.

Investigators at the University of Minnesota also performed experiments with a vaccine to treat addiction to nicotine (Keyler et al. 2008). They began by taking a group of rats and injecting them with different types of proteins—proteins that would bind to the nicotine and attract the antibodies, preventing them from passing through to the brain. The experiment had three experimental groups, each injected with a different type of binding protein. The control group was a group of rats who received no protein injections at all. After three series of vaccinations, the rats were anesthetized with dropiridol/fentanyl, and then injected with .03/ mg/kg of 6-CMUNic, 3-AmNic, and Bivalent over 10 sec via the jugular cannula. The rats were decapitated 3 minutes later and levels in the blood and brain were collected and stored at -20 degrees Celsius until processed. Serum and brain protein concentrations, nicotine protein binding parameters, and serum NicAb concentrations were compared among groups by one way ANOVA and individual comparisons were analyzed by t-test. As seen in Figure 2, the results indicated that each of the vaccines increased the total serum nicotine concentration, and reduced the nicotine concentration in the brain compared to the control group.

The results indicate that it is possible to design more than one immunological distinct hapten from a small molecule such as nicotine to inject via vaccine to bind to nicotine and prevent it from crossing the blood-brain barrier. The fact that the Bivalent showed evidence for antibodies in the blood, and lack thereof in the brain, shows the success of having the antibodies bind to the nicotine vaccine. The results show potential for using the vaccine to treat addiction for nicotine and ensure that the dopamine receptors are not affected by the drug (Keyler et al. 2008).

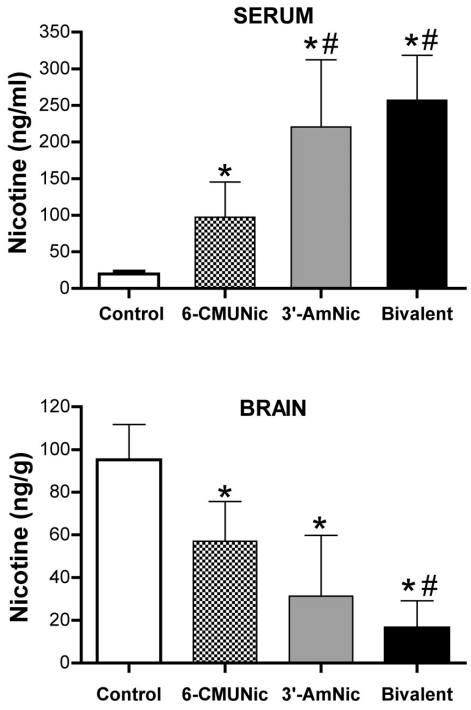

Figure 2: Results indicating the decreased nicotine levels in the blood of rats that were vaccinated, as well as the increased nicotine levels in the brains of non-vaccinated rats. Source: Keyler et al. 2008

Clinical Trials

Researchers at Maastricht University extended the studies to human subjects. In this case, the researchers evaluated the safety and immunogenicity of four doses of a nicotine vaccine in smokers and non-smokers. The subjects were in good physical and mental health. Each volunteer either received an injection of a placebo in the control group, or the vaccine in the experimental group. In this case, the

scientists were not trying to see how much nicotine reached the brain. They were attempting to measure the success of the vaccine in creating nicotine-specific antibodies. The results would lead scientists one step further in treating subjects addicted to nicotine. The subjects received a vaccination of 3'-aminomethylnicotine conjugated to detoxified Pseudomonas aeruginosa r-exoprotein A each week. At first, no difference was seen between the two groups. However, after 21 days, 7 days after the second vaccination, significant increase in the geometric mean titer (GMT) levels of nicotine-specific antibodies were observed in the smokers. Nicotine-specific antibody levels rose to a GMT of at least 8 at day 49, and at least 10.8 at day 217. With each additional vaccination, the level continuously rose. These results indicate that the immunogenicity of the vaccine was not impeded by the presence of nicotine, thus providing evidence in humans that the vaccine used may represent a feasible strategy for evoking type-specific antibodies against nicotine. With these type-specific antibodies, the body can ward off nicotine and prevent it from reaching the brain (Wagena et al. 2008).

Researchers at Yale University performed a similar experiment testing the therapeutic effects of a cocaine vaccine, using the same technique as the nicotine vaccine. The researchers used 34 former cocaine abusers as their experimental group. They were divided up and each was given a different dosage of the vaccine, 8 at 13 micrograms of the active vaccine, 10 at 82 micrograms, and 10 at 709 micrograms. Two subjects in each group represented the control group who received a placebo. Each group got an intramuscular injection for up to 2 months and was monitored for safety and antibody production for 3 months. Twenty-seven of the subjects completed the full course of three injections. However, only 24 returned for the final scheduled visit on day 84. The vaccine had no drug-related adverse effects, but three subjects at the highest dose experienced brief twitching after being injected (Martell et al. 2007).

Antibody levels were correlated with vaccine dosage and number of injections. Anti-cocaine antibodies were first detected after the second injection. The number of antibodies peaked after 3 months of treatment and then declined to baseline by 1 year. The therapeutic vaccine was well tolerated, with dose related increases in antibody levels, and a high proportion of patients recruited into the study were retained (Martell et al. 2007).

Another experiment was performed using a vaccine to treat cocaine dependence. Eighteen subjects were tested with dose-escalation over fourteen weeks. Ten subjects received four 100 mg injections over the course of eight weeks. The other eight subjects received five 400 mg injections over twelve weeks. The urine toxicologies and cocaine antibody titers were compared, three times each week.

Sixteen of the 18 subjects completed the study. The 2000 mg total dose group had significantly higher mean antibody titer response (2000 units) than the 400 mg total dose group. Despite the fact that there were relapses in both groups, the subjects said they lost the euphoric effect of cocaine at the six month follow-ups, 63% in the 400 mg and 100% in the 2000 mg groups.

The conjugated vaccine to treat cocaine addiction was well-tolerated and the antibodies were prevalent for at least six months. Additionally, the subjects who received the more intense vaccination schedule had less likelihood of using cocaine.

These experiments prove that vaccines were effective in raising the antibody level in the body, as well as preventing the drugs from reaching the dopamine

receptors. However, the experimental groups were small and the researchers did not extend the experiment to see how long the effects lasted and if the dopamine receptor levels were up-graded and normal levels restored.

Multiple pharmaceutical companies are performing vaccine clinical trials as well. The adjuncts used in the clinical trials are known as alum hydroxide or phosphate. All of the clinical trials have administered the vaccine via injection. The company Cytos has successfully completed a Phase I clinical trial involving 40 non-smoking subjects who showed no unexpected toxicities. In Phase II of the study, individuals with antibodies in the highest percentile were able to avoid relapse to cigarette consumption for longer than the subjects who received a placebo vaccine. Abstinence rates in subjects with lower antibody responses were not significantly different from those in the placebo group (Escobar-Chavez et al. 2011). This experiment proved that elevated antibody levels are effective in preventing relapse to cigarette consumption.

Cytos's nicotine vaccine program now collaborated with Novartis AG. Together they performed a double-blind placebo-controlled Phase I study evaluating immunogenicity and tolerability of the vaccine. The study contained four groups of 10 non-smoking subjects who were given different doses of the vaccine. All of the subjects evaluated responded with high levels of nicotine-specific antibodies and a long-lasting immune response. Up to half of the patients reported negative effects such as muscle aches, fever, and chills. Those symptoms disappeared within one day, and the elevated antibody level declined over time.

In Phase II of the clinical trial, a group of 341 smokers were divided: two thirds received the active vaccine and one third received a placebo. Afterwards, five injections of 100 mg of vaccine conjugate were given monthly and the subjects received counseling for the first three months. The subjects were required to abstain from smoking from week 8 to week 52 after receiving treatment. The researchers used self-reporting and biochemical markers to evaluate that the subjects were adhering to the regulations. The participants reacted as predicted. The two thirds receiving the active vaccine developed elevated levels of antibodies, while the control group did not. Though the vaccine was tolerated, there were some side effects such as flu-like symptoms. However, the effects only lasted for one day.

In May 2005, six-month results were published, and later that year, 12-month results were published. According to the results of the antibody levels, the smokers were divided into three groups: low, medium, and high responders. The high responders group had continuous abstinence after 6 to 12 months of 57% ($P=0.004$ as compared to the placebo group) and 42% respectively. The medium responders group had a result of 32% and 21% respectively, and the low responders group had 32% and 26% respectively. The relatively high continuous abstinence rate for the placebo group was 32% and 26%.

Another study Cytos performed with healthy volunteers evaluated giving 300 mg per injection as opposed to 11 mg. The higher dose induced a greater mean antibody production that was four times higher than the initial Phase II study. The company also reported new formulations reducing the incidents of fever and flu-like symptoms to about 10% as opposed to the original 60% (Escobar-Chavez et al. 2011).

The clinical trials performed by Cytos indicated the success of the vaccine in treating nicotine addiction. The subjects with increased levels of antibody production

maintained their smoking prevention and abstained from relapsing for longer periods of time. Immunization against nicotine can significantly ease some behavioral effects of nicotine. The results of these experiments suggest that immunologic intervention could have use in the treatment of tobacco dependence. However, further research and clinical trials are necessary to validate that vaccinations facilitate abstinence from nicotine use (Escobar-Chavez et al. 2011).

POTENTIAL FOR THE NICOTINE VACCINE

The nicotine vaccine certainly shows some degree of efficacy. Overall, the data indicated in the experiments and clinical trials support the vaccine in preventing nicotine from affecting the dopamine receptors. Clinically, though, the vaccine will not replace existing medication. Nicotine replacement therapy, such as bupropion and nortriptyline, will still be the main form of treatment. However, the vaccine can lessen the rewarding effects of nicotine, something which existing therapies cannot do significantly, thereby complementing current treatment (Escobar-Chavez et al. 2011).

The nicotine vaccine can also be useful in relapse prevention by blocking the effects of using a cigarette. Vaccination can also be done while the individual is still smoking, thereby preparing the individual to quit. The vaccine may also have a possible role in preventing high-risk teens from becoming completely addicted to smoking. However, that will require additional confidence and safety assurances aside from proof of efficacy.

Most importantly, vaccination can play a role in aiding individuals who are taking proactive steps to a complete recovery. Although research suggests that immunologic intervention can play an important role in treatment of tobacco addicts, the patients first need to be motivated to quit. The vaccine does not treat the non-pharmacological factors that maintain tobacco dependence. By giving the vaccine in conjunction with behavioral intervention, patients can maximize the results and may quit their nicotine-dependence.

More reports on the vaccine will be publicized within the coming year. Phase III trials and marketing launch dates for nicotine vaccines have yet to be announced. However, the results of the experiments and clinical trials performed thus far are indicative of the possibility of successfully distributing a vaccine to induce type-specific antibodies to prevent nicotine from entering the brain (Long 2011). These experiments provide a basis for creating vaccines to treat other substances as well, using the same strategy. Scientists are merely steps away from succeeding in creating an effective vaccine against nicotine, and perhaps with that success, they will attempt to create further vaccines type-specific for antibodies to bond to other addictive substances.

DISADVANTAGES/ETHICAL ISSUES

There are numerous ethical issues that arise with the possibility of producing and distributing a nicotine vaccine. Firstly, misconceptions may arise that the vaccine will give lifelong immunity against nicotine and may cause parents to vaccinate their children, and as minors, children will be unable to dissent. Some may say that parents have a right to protect their children, while others may fight this view, namely, tobacco producers. Additionally, there is a danger that people may overdose on drugs after receiving the vaccine due to their inability to feel pleasure from the drugs.

On the other hand, the vaccine used for treatment of addiction has many advantages. Most importantly, though not eliminating the cravings, the vaccine will

help the addict stick to his recovery, in that after his injection he will be free of the drug induced chemical reactions that he relied on so heavily (Kosten 2011). With this-once-a-month vaccine, the recovering addict has a stronger chance of maintaining his treatment plan, as it only takes a monthly injection to ensure that he does not feel the affects of succumbing to his desire to relapse, and thus can overcome the initial most difficult moths of addiction treatment (Long 2011). The most crucial part of any drug treatment is the prevention of relapse. With the antibodies from the vaccine remaining within the user's system for an entire month, the user will be protected from relapses throughout that time period, and hopefully remain drug-free by choice after that.

Additionally, the vaccine poses minimal danger to the subject's health and normal brain functioning. By blocking the brain from receiving the chemicals from the drugs, the user will be able to stop his behavior and control his addiction. The vaccine can also be used alongside psychological therapy because it does not affect normal brain functioning; it prevents both the vaccine and the drug from entering the brain (Long 2011). Another advantage of the vaccine is that it saves time, since it only has to be given once a month. It saves money as well, as other forms of pills, compresses and treatments may be minimized or eliminated. Though it is advisable for subjects of addiction to see a psychologist continuously, the vaccine helps prevent a relapse because they will stop using the drug once they realize it has no effect on them, thus eliminating relapse costs.

Another major advantage is that the addictive substance is not being treated with another addictive substance, drug for drug. With the vaccine, the effect of the addictive substance is being eliminated, while refraining from adding additional potentially addictive substances to the body. Traditional addiction treatments typically involve medications that mimic a drug in the brain. For example, methadone will stand in for heroine and a nicotine patch will substitute for cigarettes. Other medications block activity in the brain's reward system, such as Vivitrol injections for alcoholics and Pfizer Inc.'s Chantix pills that block the brain's pleasure receptors from being activated when people smoke. Some of these drugs function inside the brain and thus can pose potential damage to the brain. Warnings include depression and suicidal thoughts (Long 2011). On the other hand, vaccines pose no risk to normal brain functioning.

CONCLUSION

Addiction is a clear indicator of biological and biochemical psychology and the way the brain controls behavior. The brain plays a strong role in human behavior in that ultimately, addicts are craving the chemical reaction that the drug causes. Though there are many medications for addicts, psychologists have noted that the success rate of treatment for drug-abuse is unfortunately low (Koob and Moal 2001). The fact that the development of a vaccine may be able to treat addiction poses a new hope for addicts' recovery.

The idea of using the body's innate immune system functions to treat addictions is brilliant. By using antibodies, no risk is posed to the brain or normal functioning. This technique may also be implemented for other health issues that involve chemicals reaching the brain. The development of such a vaccine can be the basis for further development and treatment for other dangerous chemicals that reach the brain. Using vaccines to treat addiction is just one step in using the antibodies already in our bodies

to treat illnesses. Antibodies are G-d's army to fight disease; why not utilize them to their complete capacity?

REFERENCES

American Lung Association. 2011. LungUSA. In Finding Cures and Your Lungs. Retrieved January 17, 2012 from: http://www.lung.org/finding-cures/

Chandler RK, Fletcher BW, Volkow ND. 2009. Treating Drug Abuse and Addiction in the Criminal Justice System. The Journal of the American Medical Association. Retrieved January 17, 2012 from: http://www.ncbi.nlm.nih.gov/pubmed?term=Treating%20drug%20abuse%20and%20addiction%20in%20the%20criminal%20justice%20>.

Diana M. 2011. The Dopamine Hypothesis of Drug Addiction and its Potential Therapeutic Value. Front Psychiatry 2:64. Retrieved January 17, 2012 from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3225760/?tool=pubmed>.

Escobar-Chávez JJ, Dominguez-Delgado CL, Rodriguez-Cruz IM. 2011: Targeting Nicotine Addiction: The Possibility of a Therapeutic Vaccine. Drug Des Devel Ther 5:211-224. Retrieved January 17, 2012 from: http://ukpmc.ac.uk/articles/PMC3096537/reload=0;jsessionid=wkDh9IBsjoh2l1PSKg5T.102

Hall WD. 2005. Will Nicotine Genetics and a Nicotine Vaccine Prevent Cigarette Smoking and Smoking-Related Diseases? PLOS Medicine 2(9):e226. Retrieved January 17, 2012 from: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0020266

Hieda Y, Keyler DE, Vandevoort JT, Kane JK, Ross CA, Raphael DE, Niedbalas RS, Pentel RP. 1997. Active immunization alters the plasma nicotine concentration in rats. Journal of Pharmacology and Experimental Therapeutics 283(3):1076-1081. Retrieved January 17, 2012 from: http://www.ncbi.nlm.nih.gov/pubmed/9399979

Kenny PJ, Chen SA, Kitamura O, Markou A, Koob GF. 2006. Conditioned Withdrawal Drives Heroin Consumption and Decreases Reward Sensitivity. Journal of Neuroscience 26(22):5894-5900. Retrieved January 25, 2012 from: http://www.ncbi.nlm.nih.gov/pubmed/16738231

Keyler DE, Roiko SA, Earley CA, Murtaugh MP, Pentel PPR. 2008. Enhanced Immunogenicity of a Bivalent Nicotine Vaccine. International Immunopharmacology 8(11):1589-1594. Retrieved July 25, 2011 from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2577591/?tool=pmcentrez

Khoury MJ, McCabe LL, McCabe ERB. 2003. Population Screening in the Age of Genomic Medicine. The New England Journal of Medicine 348:50-58. Retrieved January 18, 2012. from: http://www.nejm.org/doi/full/10.1056/NEJMra013182

Koob GF, Moal ML. 2001. Drug Addiction, Dysregulation of Reward. Neuropsychopharmacology 24(2):97-129. Retrieved July 25, 2011. from: http://dionysus.psych.wisc.edu/coursewebsites/PSY411/Articles/KoobG2001a.pdf

Kosten T. 2011, June 1. Shooting Down Addiction. The Scientist. Retrieved July 25, 2011 from: http://the-scientist.com/2011/06/01/shooting-down-addiction/

Long M. 2011, May 3. Quest for Vaccines to Treat Addiction. The Wall Street Journal. Retrieved July 25, 2011 from: http://online.wsj.com/article/SB10001424052748704436004576298980739463392.html

Martell BA, Mitchell E, Poling J, Gonsai K, Kosten T. 2005. Vaccine Pharmacotherapy for the Treatment of Cocaine Dependence. Biological Psychiatry Journal 58(2):158-164. Retrieved January 17, 2012 from: http://www.biologicalpsychiatryjournal.com/article/S0006-3223(05)00493-2/abstract

Melis M, Spiga S, Diana M. 2005. The Dopamine Hypothesis of Drug Addiction. International Review of Neurobiology 63:101-154. Retrieved January 17, 2012 from: http://www.ncbi.nlm.nih.gov/pubmed/15797467

Pentel P, Malin D. 2002. A Vaccine for Nicotine Dependence: Targeting the Drug Rather than the Brain. Respiration 69:193-197. Retrieved January 18, 2012 from: http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowFulltext&ArtikelNr=63617&ProduktNr=228474

Schultz W. 2010. Multiple Functions of Dopamine Neurons. F1000 Biol Reports 2:2. Retrieved July 25, 2011 from: http://f1000.com/reports/b/2/2

Vocci FJ, Chiang CN. 2001. Vaccines Against Nicotine: How Effective are They Likely to be in Preventing Smoking? CNS Drugs 15(7):505-514. Retrieved January 17, 2012 from:

http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed&cmd=Search&doptcmdl=Citation&defaultField=Title%20Word&term=Vocci%5Bauthor%5D%20AND%20Vaccines%20against%20nicotine%3A%20How%20effective%20are%20they%20likely%20to%20be%20in%20preventing%20smoking%3F

Wagena EJ, de Vos A, Horwith G, van Schayck CP. 2008. Randomized, placebo-controlled phase 1/2 trial evaluated the safety and immunogenicity of four doses of a nicotine vaccine in smokers and nonsmokers. Nicotine and Tobacco Research 10(1):213-218. Retrieved July 25, 2011. from: http://ntr.oxfordjournals.org/content/10/1/213.full.pdf

Wise RA, Rompre PP. 1989. Brain Dopamine and Reward. Annual Review of Psychology 40:191-225. Retrieved July 25, 2011 from: http://www.annualreviews.org/action/showCitFormats?doi=10.1146%2Fannurev.ps.40.020189.001203