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Rick A. Bevins
University of Nebraska-Lincoln, rbevins1@unl.edu

Jamie L. Wilkinson
University of Nebraska-Lincoln

Sam D. Sanderson
University of Nebraska Medical Center

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Vaccines to Combat Smoking

Rick A. Bevins, Ph.D. [Professor of Psychology][1], **Jamie L. Wilkinson, M.A. [Research Assistant]**[1], and **Sam D. Sanderson, Ph.D. [Associate Professor]**[2]

[1]238 Burnett Hall, Department of Psychology, University of Nebraska-Lincoln, Lincoln, NE 68588-0308 USA

[2]School of Allied Health Professions, University of Nebraska Medical Center, 985150 Nebraska Medical Center, Omaha, NE 68198-5150, USA

Abstract

Background—Current U.S. FDA approved biological therapies for treating smoking target central nervous system processes. Although these therapies have had some success, relapse within a year is still high. Clearly additional strategies are needed to aid individuals in maintaining abstinence.

Objective & Methods—We briefly discuss promising research using vaccines to combat smoking and then identify some potentially important directions for future research.

Results & Conclusions—Immunization with a nicotine vaccine generates drug-specific antibodies that sequester some of the nicotine in peripheral circulation preventing it from entering the brain thus decreasing its addictive effects. Albeit promising, much more research is necessary to identify more efficacious vaccine designs and formulations, as well as optimal immunization regimens. A further understanding of the contributing factors to the substantial individual differences in immunogenicity to these vaccines and how to best use vaccines in combination with other treatment strategies will increase the success of intervention efforts.

Keywords

cigarette; cotinine; drug-specific antibody; immunotherapy; immune system; nicotine addiction; tobacco

Introduction

Worldwide smoking is the leading cause of preventable deaths and is a substantial personal burden to individuals (and their loved ones) suffering from smoking-related diseases, as well as a fiscal burden to society in lost worker productivity and health-care costs [1]. Although a majority of smokers are motivated to quit, without intervention nearly 95% of those that stop smoking will relapse within a year [2]. The consensus among the scientific community is that nicotine is the primary addictive compound in tobacco products. Given the tenacity of the addiction and the extent of its harm, advances in treatment that increases long-term cessation rates are needed. To date, all United States FDA approved biological therapies (varenicline, bupropion, nicotine replacement therapy) target central nervous system (CNS) processes believed to be involved in nicotine dependence.

In contrast, a recent treatment advance showing promise in preclinical research, as well as in early treatment trials, uses an immunological approach (i.e., vaccine) to prevent nicotine

Correspondence to: rbevins1@unl.edu, phone: 402.472.1189, fax: 402.472.4637.

from entering the CNS (e.g.,[3–5]). A vaccinated individual will have antibodies for nicotine (see Figure 1). If that individual smokes, some portion of the nicotine in periphery (blood and extracellular fluid) will be sequestered by these antibodies. Because antibodies are too large to permeate the blood-brain-barrier, less nicotine enters the CNS thus decreasing its impact on brain systems involved in addiction (e.g., mesocorticolimbic system). For the generation of an immune response to nicotine, a nicotine vaccine must activate and engage the necessary cellular components of the innate and acquired arms of the immune system. Because the nicotine molecule is too small to engage these processes itself, this has been accomplished to date by an immunoconjugate design in which multiple nicotine haptens are conjugated (i.e., linked) to a carrier protein. To potentiate the immune response, this conjugate vaccine is admixed with an adjuvant (e.g., alum) for the final vaccine formulation [6,7].

Such vaccine designs have clearly demonstrated utility in inducing the anti-nicotine antibody responses necessary for alteration of nicotine-induced psychoactive effects in rodents [4,8], and the results from early initial treatment trials with several different vaccine designs show therapeutic promise [9–11]. Immunotherapies for smoking cessation might have some advantages over pharmacotherapies [7,12]. A well-designed vaccine will have good specificity for nicotine over related endogenous ligands (e.g., acetylcholine). This specificity combined with the fact that vaccines target the nicotine molecule rather than the CNS processes involved in the addiction translates into fewer side effects [7]. Medications for smoking cessation (e.g., bupropion, varenicline) require patients to follow daily instructions for effective treatment. A vaccine approach using active immunization processes, however, requires an initial vaccination and several follow-up boosts. Fewer side effects, along with a less effortful treatment protocol (show up for a few appointments) may enhance patient compliance to treatment [7,12]. A comprehensive review of the research or immune system processes involving vaccines designed for treating smoking is beyond the goal and scope of a Future Perspectives article. Thus, we refer the reader to the following recent reviews [4,6,7] for excellent and detailed discussion of vaccines to combat drug addiction.

Notable Considerations

The advantages of a vaccine approach just noted prompt discussion of some notable findings from preclinical and clinical research that require consideration as possible areas for future research advances into the efficacy of vaccines for treating smoking. For instance, the immunogenicity of a vaccine formulation varies widely across individuals and, not surprisingly, the efficacy of any particular vaccine appears directly related to its ability to raise drug-specific antibodies [9,10]. A better understanding of design and formulation features of hapten-based vaccines, as well as how these features engage the immune system and interface with differences between individuals and responsivity to immunization, will improve future vaccines (cf. [6]). One idea that emerges from this discussion of individual variability in immunogenicity is the possible use of combinations of different vaccine designs to increase their overall efficacy. Related to this discussion is the slow onset of current active immunization protocols, which typically require several temporally spaced boosters before therapeutically-relevant levels of nicotine-specific antibodies are observed. Indeed, this lag time from treatment to onset of effectiveness makes active immunization more likely to be useful for prevention of relapse rather than promoting initial cessation (7,8). Passive immunization with a monoclonal antibody has been suggested as a solution to fill this lag; that approach, however, will likely be more expensive and have increased risk of side effects such as allergic reactions [4,6]. Research advances elucidating the processes underlying the efficiency and proficiency of each vaccination to induce a drug-specific immune response, as well as improve the quality of the antibody produced (e.g., increased

binding affinity, longer half-life, etc.) will enhance the potential utility of vaccines for the treatment of smoking. Given that nicotine does not appear to have immunogenic effects alone, continued effectiveness of vaccination treatment requires periodic boosters. Thus, research should also focus on designs and vaccination regimens that lead to a more prolonged immune response.

As noted earlier, the efficacy of vaccines against nicotine appears to rely on preventing at least some portion of nicotine from entering the CNS where it acts on neurobiological processes underlying drug addiction and dependence. Several individuals have speculated that antibodies that sequester this portion of nicotine early, before it reaches the CNS, will be more effective since these early effects appear to mediate reward and other psychoactive processes maintaining smoking [4–6]. We agree with this conjecture. However, considering that vaccine effectiveness relies on its ability to function as a pharmacokinetic antagonist suggests some important questions regarding individual differences. For example, research with human participants indicates that women are less sensitive to the rewarding effect of nicotine than men, and that social factors appear particularly important for women [13]. This finding suggests that nicotine vaccines might be more effective in men than women. More generally applied, a vaccine might be better suited to individuals for whom the pharmacological effects of nicotine are critical for maintenance of smoking—regardless of sex. Alternate interventions may be more effective for those individuals for which cognitive, behavioral, and social factors are more important. Indeed, the very nature of a vaccine approach means that it does not directly act on CNS processes mediating implicit or explicit affective or cognitive processes involved in smoking. As such, a vaccine will likely be most effective when used in combination with pharmacological and/or cognitive-behavioral interventions [5,12]. Clearly, research identifying factors that promote smoking for an individual (age of onset, sensitivity to nicotine, etc.) along with research on effective combinational treatment approaches that include vaccination will likely improve smoking cessation efforts.

Expert Opinion

Clearly, much research is still needed to fully appreciate how nicotine vaccines are effective, as well as what factors will determine effectiveness within and across individuals. Preclinical and early treatment studies have provided proof-of-principle examining a relatively small number of variables relevant to the efficacy of vaccines for treating smoking. We believe that much more programmatic and parametric research is needed on vaccine design, formulation, and immunization schedule, as well as their impact on nicotine-specific antibody production and any accompanying changes in the pharmacokinetic and pharmacodynamic effects of nicotine. This research will likely include how the nicotine hapten is spaced and/or oriented on the carrier protein, the optimal number of haptens per carrier protein, how the nicotine is conjugated to the carrier protein, alternates to carrier protein immunoconjugate designs such as the use of peptide-based molecular adjuvants [14], and how immunization variables such as number and spacing affect vaccine efficacy [6,7].

The present paper has focused on vaccines against nicotine because the bulk of the research effort for vaccines to combat smoking has targeted nicotine—the primary addictive constitute of tobacco. However, other constitutes of tobacco and/or major metabolites of nicotine (e.g., MAO inhibitors, nornicotine, cotinine, etc.) are thought to contribute to tobacco addiction (cf. [15,16]). Indeed, a recent paper has provided support for the potential utility of a vaccine for cotinine, a major metabolite of nicotine [15]. The idea behind a cotinine vaccine is based on research indicating that this metabolite functions to antagonize the effects of nicotine in the CNS. By doing so, cotinine decreases the relative efficacy of nicotine replacement therapy to alleviate withdrawal symptoms—an important factor in

relapse. Cotinine-specific antibodies from vaccination sequester cotinine in the periphery prohibiting its entry into the CNS. The net result of this sequestering would be to allow more nicotine to act in key brain areas involved in withdrawal and supposedly increase the efficacy of nicotine replacement therapy [15]. This is an interesting proposition that requires much more research. Further, this proposition suggests that other psychoactive constitutes of tobacco and/or metabolites of nicotine (e.g., nornicotine) might be therapeutic targets [16].

Writers on the therapeutic uses of vaccines for smoking are virtually unanimous in considering it as an adjunct with other cognitive-behavioral and/or pharmacological treatments (e.g.,[4,5,12,15]). This recommendation recognizes that centrally mediated alterations in affect and cognition resulting from quitting smoking are not targeted by vaccines. Despite this congruous opinion, there has been little empirical effort to examine the effectiveness of combination therapies. As clinical trials with vaccines focus more on smoking cessation and its associated constructs (e.g., withdrawal, cravings, anhedonia) as outcome variables, we predict that research assessing the vaccine in combination with, say, bupropion or varenicline will be conducted. Such combinational treatment regimens might be especially helpful in relapse vulnerable populations that may be more likely to try to surmount the ability of antibodies to sequester nicotine. Of note, this compensatory smoking has yet to be reported in early treatment trials. However, these initial studies include participant exclusion criteria that might not allow sufficient sampling of vulnerable populations (e.g., alcoholics, schizophrenics, etc.).

Chronic nicotine-dependent smokers seeking help to quit or not to relapse are the primary target for immunotherapy. However, several authors have noted that vaccines might be used as a prevention technique in youths that do not smoke or are experimenting [5,6]. If this suggestion is seriously considered, we hope that extraordinary empirical effort would be expended not only on “standard” safety, but on more subtle biological effects that could significantly affect later behavior. For instance, the pharmacokinetic and pharmacodynamic effects of nicotine in a vaccinated adolescent experimenting with tobacco will differ from a non-vaccinated individual—antibodies sequestering nicotine slow metabolism, create a longer elimination half-life, and alter CNS effects. Although these alterations may be desirable in dependent individuals, the impact of such alterations is unclear in someone that has had little or no experience with nicotine. In general, retrospective studies suggest that blunting the early negative (nausea) and/or positive (buzz) effects of the first cigarette might have protective effects [17,18]. However, these are self-report studies of a past experience. Furthermore, the long-term neurobiological effects of the altered pharmacodynamics are unknown. Considering that nicotine acts in brain systems regulating learning, feeding, anxiety, addiction, etc., it will be very important to ensure that a preventive strategy with a vaccine does not unintentionally increase vulnerability to other addictions (alcohol, gambling) or mental health issues.

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Abbreviations

CNS	central nervous system

FDA	Food and Drug Administration
MAO	monoamine oxidase

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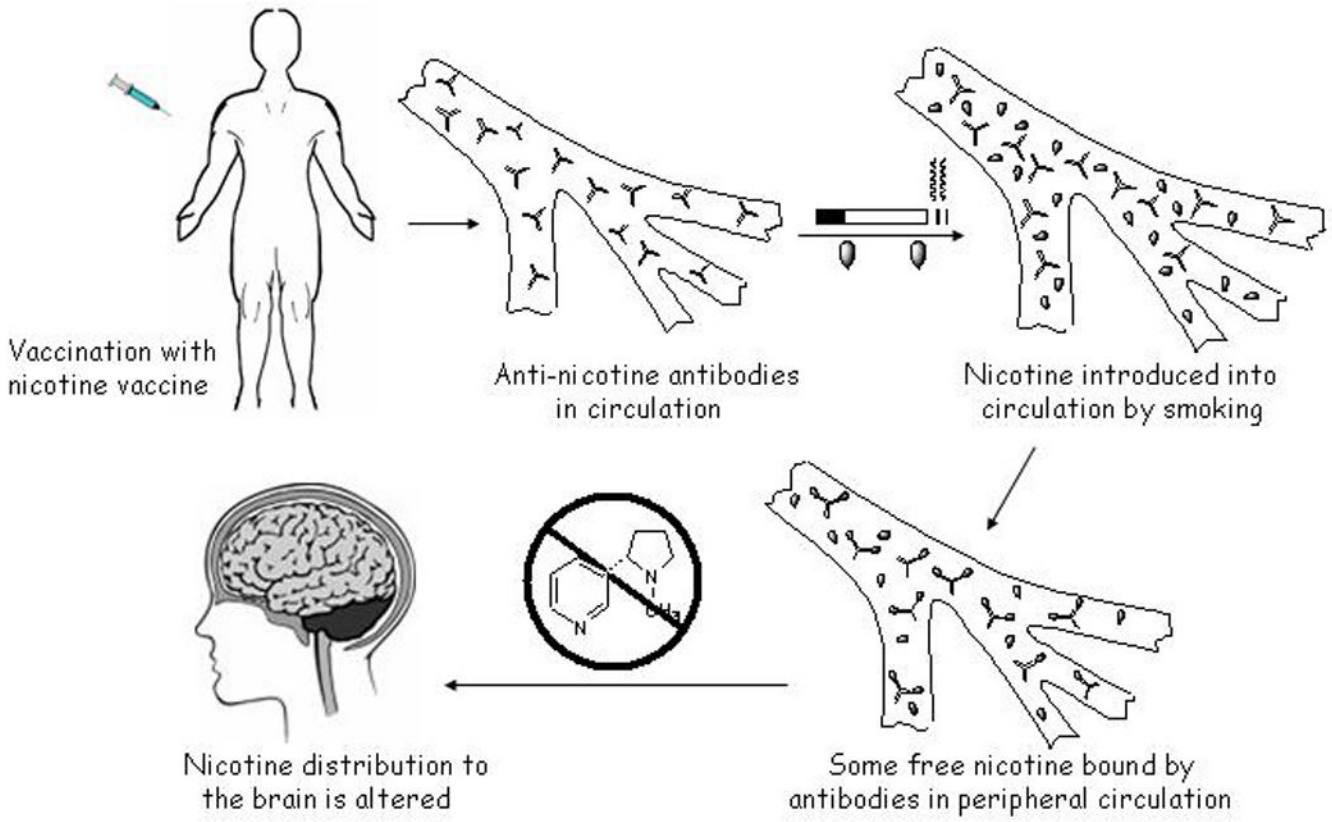

Figure 1.

This cartoon diagrams the rationale and mechanism behind a vaccine for the treatment of nicotine use (e.g., smoking). An individual is vaccinated according to some empirically determined immunization schedule. Immunization with the nicotine vaccine will activate the immune system to produce drug-specific antibodies. If an immunized individual then uses a nicotine-containing product such as cigarettes, some portion of the nicotine in serum and extracellular fluid will be sequestered by the antibodies. Although nicotine readily passes through the blood-brain-barrier, antibodies are too large to do so resulting in less nicotine entering the brain. This decreases nicotine's impact on brain systems involved in addiction (e.g., mesocorticolimbic system). Especially effective vaccines will be ones that raise a robust immune response with the fewest immunization boosts, produce antibodies that are highly specific for nicotine, and include a binding affinity that allows the initial introduction of nicotine into the periphery to be sequestered very quickly.