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Review

Progress in the Development of Immunotherapies for Substance Use Disorders

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ABSTRACT

Substance use disorder (SUD) and drug addiction serious mental health problems worldwide. Recent neuroscience studies have supported the development of new treatment approaches through the identification of novel signaling pathways and the discovery of new drug targets. Addiction vaccines have emerged as a promising treatment option for SUDs. While standard addiction treatments rely on behavioral interventions and pharmaceutical therapy, addiction vaccines provide a novel and potentially transformative technique for preventing relapse and promoting long-term recovery. Monoclonal antibodies, enzymes, and gene therapies for SUD are also being studied. Unlike small molecule medications that directly interact with brain receptors, biologics designed for SUD are larger molecules that cannot penetrate the blood-brain barrier. Instead of acting on brain receptors, these biologics target the drug itself, aiming to block its distribution to the brain and diminish its impact on the central nervous system (CNS). By preventing the drug from reaching the brain and blunting its effects on the CNS, these biologics offer a different approach to treating SUD compared to traditional medications that directly interact with brain receptors. This review explores emerging patterns in the advancement of immunotherapies for SUD, specifically referred to as addiction vaccines.

Keywords: Addiction, cocaine, nicotine, opioids, vaccines

Approximately 83.4 million or 29 % of adults (aged 15–64) in the European Union are estimated to have ever used an illicit drug up to 2022, with more males (50.5 million) than females (33.0 million) according to European Monitoring Centre for Drugs and Drug Addiction.[1] Also, in the United States according to the National Institute of Mental Health, there are 20.2 million adults who have a substance use disorder (SUD) by 2019.[2] The fascination with SUDs continues to grow, despite the clear and undeniable negative impacts on mental, physical, social, and economic well-being. Regrettably, even after an attempt by individuals to control or quit their substance abuse, the harmful repercussions persist and wreak on their lives for an extended period of time.[3] In the 1970s, scientists began to investigate how addictive molecules such as cocaine, heroin, and methamphetamines, as well as nicotine, may be changed to induce an immunological response.[4] This review examines new trends in the development of SUD immunotherapies simply addiction vaccines.

There are two major mechanisms thought to explain addiction. The changed set-point model of addiction suggests that addiction occurs when the brain's reward system is rewired, leading to a belief that pleasure can only be experienced with the drug and that happiness is unattainable without it. This model proposes that the internal set point is altered, causing a lack of dopamine release during pleasurable activities in the absence of opioids. As a result, individuals become reliant on the drug to experience pleasure and perceive it as necessary for achieving happiness.[5] The cognitive deficits model proposes that individuals with addictive tendencies have preexisting abnormalities in the prefrontal cortex (PFC), a brain region responsible for regulating judgment, planning, and executive functions. In individuals with addictive tendencies, the PFC is believed to be defective.[6] Specifically, the inhibitory signals sent from the PFC to the ventral tegmental area

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dopamine neurons are impaired, making it difficult for these individuals to restrain their impulsive desire to use drugs. Research indicates that heroin users may have a predisposition to addiction due to these PFC alterations, which can be further exacerbated by chronic drug use.[7]

Astrocytes, which are cells in the central nervous system (CNS), play a crucial role in modulating brain function. They form numerous connections, up to 30,000, with neighboring cells. One of their important functions is regulating the neurotransmitter glutamate, which is involved in the pharmacodynamics of opioids. In normal conditions, astrocytes actively remove excess extracellular glutamate from synapses.[5] They achieve this through two transporters called excitatory amino acid transporter (EAAT)-1 and EAAT2, which help uptake excessive glutamate and optimize neuronal activity. However, when opioids influence the system, the function and expression of glutamate transporters in astrocytes are altered. This leads to acute and chronic dysregulation of homeostasis, disrupting the balance of glutamate levels in the brain.[5,8]

Traditional SUD treatment approach has focused on small molecules as active substances that cross the blood-brain barrier showing their effect on molecular targets and inducing changes in the brain. However, recent developments in biotechnology, immunology, and neuroscience, have led to emerging new approaches for the treatment of SUDs and drug overdose. In many areas of medicine, biologics have shown extensive health benefits, especially in oncology. Different biological methods are currently under the scope of developing suitable SUD treatment besides traditional approaches such as vaccines, monoclonal antibodies, and enzymes. All biological approaches act through a common mechanism: they either aim to prevent or slow down the entry of a substance of abuse into the CNS. In particular, vaccines stimulate the immune system to produce antibodies against a specific addictive molecule.[9,10]

Studies show that achieving clinically effective antibody responses relies on the optimal activation of both antigen-specific naive B and T cell populations which, in the presence of antigen-specific CD4+ T cells, germinal centers (GC) are formed within the lymph nodes and spleen. These GCs play a crucial role in generating memory B cells and antibody-secreting B cells. The memory B cells retain the information about the specific antigen, while the antibody-secreting B cells produce antibodies that are specific to the antigen.[11,12] Therefore we can propose that differences in the population size of vaccine-specific B or T cells play a role in determining the individual efficacy of SUD vaccines.[11]

NICOTINE

Available Food and Drug Administration-approved smoking cessation therapies include nicotine replacement therapy, antidepressant medicines (bupropion and nortriptyline), and nicotinic cholinergic partial agonists (varenicline) through different administration routes. In order to elicit a specific immune response effectively, nicotine which is a small molecule, needs to be conjugated to a larger carrier molecule.[13]

Second half of the 1990s and early 2000s when the first nicotine conjugate vaccine studies were conducted in animals. The idea behind these vaccines is to produce antibodies attaching to nicotine molecules and prevent them from binding to nicotinic receptors. NicVAX (Nabi Biopharmaceuticals) and NicQβ (Cytos Biotechnology) are the products that have early-stage promising results. Studies show a significant correlation between high titers of anti-nicotine antibodies and long-term smoking abstinence.[9] NicVAX, which advanced to Phase III clinical trials, was composed of a nicotine derivative (3'-amino-methyl-nicotine), which was conjugated to a detoxified protein called *Pseudomonas aeruginosa* exoprotein A.[4]

In recent years, new strategies have arisen to increase the effectiveness of nicotine vaccines. Carrera et al.[14] studied enantiomeric vaccines which include only a single enantiomer of (-) nicotine haptens conjugated with protein carriers and they managed to reduce to effect of nicotine in the brain compared to the control group. Multivalent vaccines are another strategy in the area. The molecular design of the vaccine aimed to boost immunological response by increasing hapten density on the carrier protein. New haptens are still being studied by different companies. Adjuvant use is also common in the increment of antibody titers in the blood. Fraleigh et al.[15] evaluated the outcomes of the Adjuvant Finlay Proteoliposome 1 (AFPL1), a natural proteoliposome isolated from the *Neisseria meningitidis* vesicle membranes. AFPL1 was used in the formulation of nasal vaccine 3`AmNic-KLH. This vaccine formulation produced antibodies that prevent nicotine from passing through the blood-brain barrier. Capsid proteins of some viruses like adenovirus type 5 E1-E3 can be also used to increase the efficacy

of nicotine vaccines. The use of nanoparticles is the last strategy in the development of a nicotine vaccine. Recently, it was reported on the usage of Poly(D,L-lactic-co-glycolic acid) (PLGA)/poly (lactic acid) (PLA) nanoparticles to create nanovaccines, in which nicotine was covalently attached to the terminal ends of PLA-PEG to create copolymers.[16]

OPIOIDS

Opioid vaccine development has been facing a variety of problems due to numerous opioid products on the market, their role in the treatment of specific conditions, and the active metabolites of the compounds. Three separate psychotropic metabolites, including morphine, are produced when heroin breaks down. Consequently, morphine and heroin were initially the focus of the development of an addiction vaccine.[4] Anton and Leff[17] at the National Institute of Psychiatry in Mexico treated the immunogenic protein tetanus toxoid with 6-(N-trifluoroacetyl)caproic acid succinimide in 2006. This compound combines with the amino group of lysines to produce a long spacer arm with a latent amino group. The rats developed large amounts of antibodies that were highly specific for heroin and morphine. The specificity against a single opioid with activity across extremely similar analogs, which may not be responsive to the whole range of opioid ligands, may place restrictions on vaccination techniques. Illicit opioids may contain a complicated mixture of opioids, and hence an individual opioid vaccine may not be totally protective. For example, the analgesic potency of fentanyl is 30 to 50 times greater than heroin, and a lesser amount of the mixture can have the same euphoric effects as heroin alone while costing considerably less to produce.[18]

In studies conducted on mice and rats, a potential fentanyl vaccine was evaluated, which comprised a fentanyl-based hapten linked to either native keyhole limpet hemocyanin (KLH) or GMP-grade subunit KLH (sKLH) carrier proteins using a tetraglycine linker. The results showed that this vaccine was successful in acutely reducing the distribution of fentanyl to the brain and mitigating fentanyl-induced antinociception (reduced sensitivity to pain). These findings suggest that the vaccine holds promise as a means of attenuating the effects of fentanyl by reducing its presence in the brain and counteracting its pain-relieving properties. Furthermore, the vaccine was efficient in alleviating respiratory depression in rats given increasing cumulative doses of fentanyl up to 0.1mg/kg.[19] Preliminary data indicates that the convergence of the coronavirus disease 2019 (COVID-19) pandemic and the opioid epidemic has led to an increased risk of hospitalization and negative outcomes in individuals with opioid use disorder and those undergoing chronic opioid treatment who contract COVID-19.[20]

After the emergence of the Omicron strain and its various subtypes, the risk of breakthrough infections was notably elevated in fully vaccinated individuals with SUD compared to those without SUD. The data revealed a 22.5% risk of hospitalization and a 1.6% risk of fatal outcomes among fully vaccinated patients with SUD.[21]

COCAINE

Cocaine has the distinction of being one of the world's oldest and most widely used drugs. Throughout history, native Inca populations in South America chewed coca plant leaves to increase their endurance during physically difficult tasks performed at high altitudes which is a tradition that lasted thousands of years.[22] Due to the alarming statistic that approximately one in six individuals who use cocaine develop a dependency on the drug, coupled with the absence of viable pharmacological remedies for example methadone treatment for heroin addiction, there is a pressing demand for novel interventions such as anti-cocaine vaccines. These vaccines could potentially offer new methods for addressing and combating cocaine addiction.[23]

Cocaine enters the body through four different routes such as sniffing, smoking, intravenous injection, and oral delivery. After cocaine is taken up by these internalization routes, cocaine molecules enter the circulatory system and easily cross the blood-brain barrier entering the brain. Upon reaching the brain, cocaine initiates the activation of the dopamine neurotransmitter. In the case of cocaine, this interaction disrupts the normal recycling process of dopamine, resulting in an accumulation of dopamine within the cells. This surplus of dopamine is responsible for the intense euphoric sensation that is often observed after consuming cocaine.[22]

Furthermore, cocaine ingestion produces a range of systemic effects throughout the body. These effects include dilated pupils, heightened energy levels, increased body temperature and blood pressure, feelings of nausea, restlessness, and the potential occurrence of hallucinations or paranoid thoughts. These are just a few examples of the multifaceted physiological and psychological

responses associated with cocaine use.[24] Similar to other addictive compound vaccines, vaccination increases the formation of anti-cocaine antibodies by mixing an antigenic carrier with cocaine, forming a compound that is too big to cross the blood-brain barrier, lowering the euphoric high and rewarding benefits of cocaine usage.[25]

Studies have shown that when mice and people are given the cholera toxin B succinylnorcocaine (CTB-SNC) conjugate vaccine, they produce anticocaine antibodies that are specific for biologically active cocaine molecules. Notably, these antibodies do not bind to benzoylecgonine, a key inactive metabolite of cocaine that has a longer half-life than the original substance. The fact that anticocaine antibodies selectively attach to active cocaine molecules rather than inactive metabolites underscores the potential effectiveness of the vaccine and specificity in targeting the pharmacologically active form of cocaine.[26]

Additionally, flagellin, which is a protein found in certain bacteria, has been demonstrated to trigger an innate immune response upon binding to toll-like receptor 5 (TLR-5) and interacting with macrophages. This interaction activates intracellular NOD-like receptor C4 (NLRC4) inflammasome, resulting in the production of pro-inflammatory cytokines. The activation of this pathway leads to the release of various molecules that promote inflammation and immune responses within the body.[27] Conjugation of the protein and slightly modified cocaine hapten with the addition of alum adjuvant, the vaccine has demonstrated the ability to activate immune signaling through multiple pathways. These pathways include the NLRC4 inflammasome, TLR-5, and phagolysosome. By engaging these different pathways, the vaccine elicits a potent and dose-dependent immune response. This indicates that the vaccine can effectively trigger various components of the immune system, enhancing the overall immunogenicity and strength of the immune response.[28-30]

In conclusion, addiction vaccines represent a promising method in the treatment of several SUDs. Addiction vaccines also hold the potential to revolutionize addiction treatment by prolonging the dosing, reducing craving, relapse, and more. Combination with behavioral and pharmacological methods can enhance the effectiveness of the quitting programs. They may aid in the prevention of drug initiation in vulnerable populations, such as adolescents, by diminishing the rewarding effects of drugs and therefore lowering the likelihood of developing addictive behaviors. Furthermore, the broad adoption of addiction vaccines could reduce the need for long-term addiction treatment and rehabilitation services, easing the burden on healthcare systems. Addiction vaccine development has faced obstacles, including the complexity of targeting many substances and the requirement for long-term effectiveness. Recent advances in vaccination technology and understanding of the immunological response, on the other hand, have brought us closer to effective remedies. In order to trigger an immune response against relatively small addictive molecules, they need to be combined with larger molecules like bacterial proteins. Clinical trials for nicotine, cocaine, heroin, and methamphetamine addiction vaccines have yielded promising results, demonstrating reductions in drug use and relapse rates.

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