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RESEARCH HIGHLIGHT

Utility of fentanyl vaccines: unique challenges posed by preventing opioid overdose and treating opioid use disorder

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Significantly contributing to the opioid overdose crisis is the dramatic increase in the number of overdoses that are caused by fentanyl and its analogues. Fentanyl is a synthetic opioid that is more potent than heroin and is relatively easier and cheaper to produce. Some individuals purposely acquire fentanyl-laced products (e.g., heroin) because of their potentially greater potency, whereas many individuals are unaware of the adulteration of heroin with fentanyl. Therefore, the development of vaccines that target fentanyl appears to have great potential as an adjunct for preventing fentanyl-induced overdoses.

In the current issue of *Neuropsychopharmacology*, Townsend et al. [1] reported a time course of efficacy for a fentanyl-tetanus toxoid conjugate vaccine designed to induce the production of peripherally circulating antibodies against fentanyl in rats, thus preventing fentanyl from reaching the brain. Following vaccine treatment at weeks 0 and 3, the authors observed maximal antibody titers in week 5, with a slow decay of titers across subsequent weeks until week 17, at which point a "booster" vaccine treatment was given. The booster rapidly returned titers to previous peak levels. To determine the functional effects of vaccination, the authors tested the rats for fentanyl-induced antinociception and the reinforcing effects of fentanyl. The vaccine significantly reduced fentanyl-induced antinociceptive effects in an antibody titer-dependent manner (at peak effect, a 24-fold shift). The authors also observed an antibody titer-dependent suppression of intravenous fentanyl self-administration, with self-administration almost abolished at week 5 when titers were highest. These results indicate that the vaccination was very effective in preventing the binding of fentanyl to μ-opioid receptors in the central nervous system (and perhaps periphery) that mediate fentanyl-induced antinociception and fentanyl's reinforcing effects.

These preclinical results are exciting because a fentanyl vaccine strategy could represent an effective tool to prevent fentanyl overdose in humans. The advantages of such a vaccine include a long half-life and the avoidance of interactions with endogenous opioid function. However, several hurdles to an effective vaccine-based prevention strategy for overdose still need to be overcome. First, there are several fentanyl analogues (carfentanil, sufentanil, valerylfentanyl, etc.). Although a fentanyl vaccine could theoretically "neutralize" several structurally related fentanyl analogues [2], the immunological response may fail to target fentanyl analogues with more dissimilar chemical structures. Second, several active fentanyl analogue metabolites are produced through complex metabolic pathways, have varying chemical structures [3, 4], and may not be targeted by the immunological response. Third, many new synthetic opioids are chemically unrelated to the structure of fentanyl. Manufacturers are constantly producing novel and potent opioids with various chemical structures. Thus, blockade of the effects of fentanyl, fentanyl analogues, fentanyl metabolites, and other μ-opioid receptor agonists would be more effectively achieved by the blockade of μ-opioid receptors with naltrexone, a μ-opioid receptor antagonist that has been approved for the treatment of opioid use disorder (OUD). However, some disadvantages of naltrexone need to be considered. Chronic naltrexone administration alters endogenous opioid function and may cause the sensitization of opioid receptors, which could enhance overdose risk upon the cessation of treatment.

Beyond overdose prevention, what might be the utility of a fentanyl vaccine for the treatment of OUD? Drug addiction is a multifaceted, chronic and relapsing disorder that is hypothesized to involve the dysregulation of reward and stress circuitries that motivates drug taking and seeking. A vaccine increases the "price" for the target drug by decreasing its potency (i.e., more drug must be purchased and consumed to achieve the same effect). Achieving compliance with vaccinations may thus be a major issue in a population that is highly motivated to take drugs. In addition, a vaccine does not alter the "price" of a multitude of alternative opioids (and nonopioid drugs) that are available. Thus, vaccinated individuals with OUD would have a higher risk of misusing other opioids and/or nonopioid drugs in an effort to circumvent the vaccine (i.e., a substitution effect).

In an individual who is highly motivated to abstain from drugs, the vaccine could be proposed as an adjunct therapy to maintain abstinence. However, individuals in protracted abstinence (e.g., 6 months of incarceration) may experience powerful physical (somatic) and emotional (motivational) signs of opioid withdrawal when facing environmental stimuli that had been previously conditioned with such negative emotional states during acute opioid withdrawal (Fig. 1; [5]). These symptoms are hypothesized to contribute to the high rates of relapse and also maintain drug seeking and taking in humans with OUD and in rats [6]. Without treating the underlying intense motivational effects that are precipitated by exposure to contexts, cues, stressors, or drugs (i.e., μ-opioid receptor agonists that are not targeted by vaccines), a vaccine would likely have no effect on the ability of these stimuli to trigger drug relapse via vaccine circumvention [7, 8]. Therefore, vaccination against fentanyl or any other drug of abuse might be minimally effective as a long-term strategy to treat substance use disorders.

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The patient was a 28-year-old man with a 10-year history of narcotic addiction. He was married and the father of two children. He reported that, while addicted, he was arrested and incarcerated for 6 months. He reported experiencing severe withdrawal during the first 4 or 5 days in custody, but later, he began to feel well. He gained weight, felt like a new man, and decided that he was finished with drugs. He thought about his children and looked forward to returning to his job. On the way home after release from prison, he began thinking of drugs and feeling nauseated. As the subway approached his stop, he began sweating, tearing from his eyes, and gagging. This was an area where he had frequently experienced narcotic withdrawal symptoms while trying to acquire drugs. As he got off the subway, he vomited onto the tracks. He soon bought drugs, and was relieved. The following day he again experienced craving and withdrawal symptoms in his neighborhood, and he again relieved them by injecting heroin. The cycle repeated itself over the next few days and soon he became readdicted.

- (O'Brien 1975, p. 533).

Fig. 1 O'Brien [5] demonstrated conditioned opioid withdrawal in humans in a laboratory experiment. This excerpt from the study provides a naturalistic description of the way in which re-exposure to conditioned stimuli, independent of the pharmacological effects of the drug, may powerfully motivate drug seeking and taking long into drug abstinence. Opioid use disorder is thought to involve the dysregulation of brain reward and stress systems that contribute to negative emotional states. These motivational withdrawal symptoms can be precipitated by internal and external conditioned withdrawal cues, persist well beyond physical (somatic) withdrawal symptoms, and powerfully motivate drug seeking and taking in an effort to alleviate these negative emotional states. A vaccine that targets fentanyl to block access of the drug to the brain could play a critical role in preventing overdoses that are produced by heroin that is laced with the potent opioid fentanyl. However, this approach would be expected to have little effect on key features of opioid use disorder that motivate drug-taking behavior

In summary, Townsend et al. [1] provide evidence of a highly effective fentanyl vaccine. Such a vaccine strategy has great potential as an adjunct for preventing fentanyl-induced overdoses. However, vaccine strategies must evolve as fast as the rapidly increasing production and distribution of highly potent synthetic opioids with diverse chemical structures. Finally, because of the lack of direct effects of a vaccine on the brain mechanisms that drive drug seeking and taking, vaccination could perhaps best be used as an adjunct to pharmacological and psychosocial treatments that target the underlying causes of drug-motivated behavior to increase the likelihood of successful treatment.

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ADDITIONAL INFORMATION

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REFERENCES

1. Townsend, A. E., Blake, S., Faunce, K. E., Hwang, C. S., Yoshihiro, N. Zhou, B., & Banks, M. L. Conjugate vaccine produces long-lasting attenuation of fentanyl vs. food choice and blocks expression of opioid withdrawal-induced increases in fentanyl choice in rats. Neuropsychopharmacology. 2019. https://doi.org/10.1038/s41386-019-0385-9.
2. Bremer PT, Kimishima A, Schlosburg JE, Zhou B, Collins KC, Janda KD. Combatting synthetic designer opioids: a conjugate vaccine ablates lethal doses of fentanyl class drugs. Angew Chem Int Ed. 2016;55(11):3772–5. https://doi.org/10.1002/anie.201511654.
3. Wilde M, Pichini S, Pacifici R, Tagliabracci A, Busardò FP, Auwärter V, et al. Metabolic Pathways and Potencies of New Fentanyl Analogs. Front Pharmacol. 2019;10:238. https://doi.org/10.3389/fphar.2019.00238.
4. Jannetto PJ, Helander A, Garg U, Janis GC, Goldberger B, Ketha H. The fentanyl epidemic and evolution of fentanyl analogs in the United States and the European Union. Clin Chem. 2019;65(2):242–53. https://doi.org/10.1373/clinchem.2017.281626.
5. O'Brien CP. Experimental analysis of conditioning factors in human narcotic addiction. Pharmacol Rev. 1975;27(4):533–43. http://pharmrev.aspetjournals.org/content/pharmrev/27/4/533.full.pdf.
6. Carmack, SA, Keeley, RJ, Vendruscolo, JC, Lowery-Gionta, EG, Lu, H, Koob, GF, et al. Heroin addiction engages negative emotional learning brain circuits in rats. J Clin Investig. 2019;130:125534. https://doi.org/10.1172/JCI125534.
7. Schlosburg JE, Vendruscolo LF, Bremer PT, Lockner JW, Wade CL, Nunes AA, et al. Dynamic vaccine blocks relapse to compulsive intake of heroin. Proc Natl Acad Sci USA. 2013;110(22):9036–41. https://doi.org/10.1073/pnas.1219159110.
8. Reiner DJ, Fredriksson I, Lofaro OM, Bossert JM, Shaham Y. Relapse to opioid seeking in rat models: behavior, pharmacology and circuits. Neuropsychopharmacology. 2018;44:465–77. https://doi.org/10.1038/s41386-018-0234-2.