Researchers find a way to combat pharmacoterrorism

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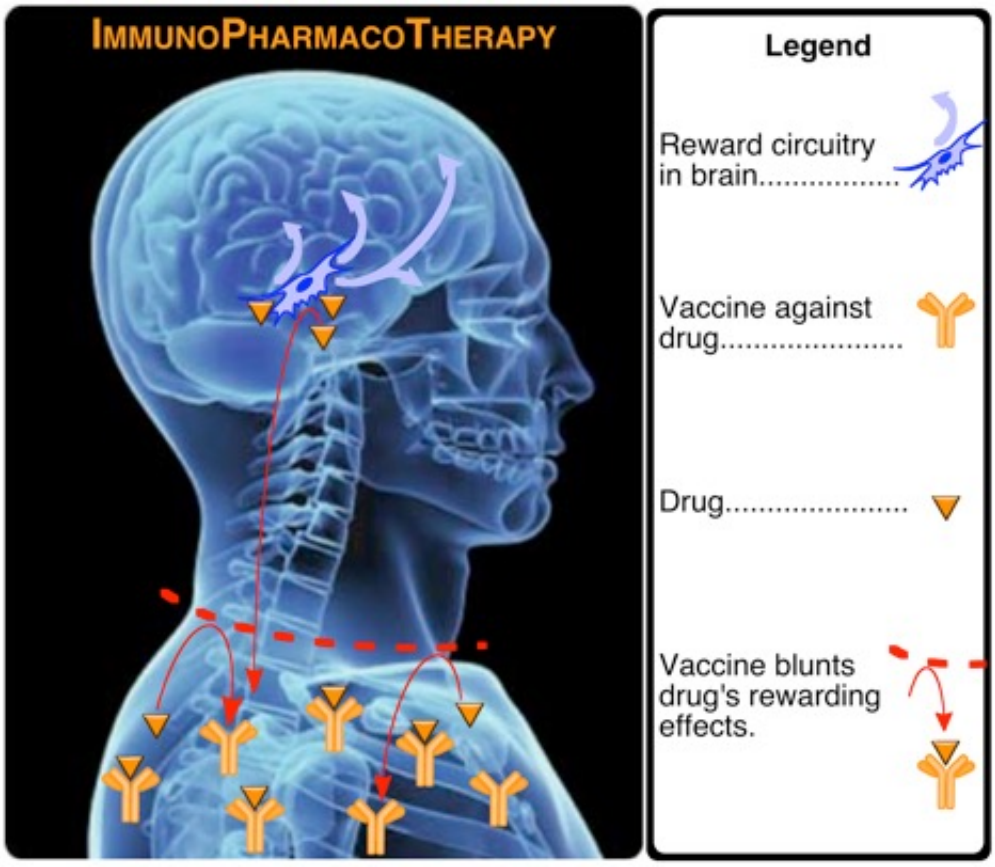

The process of drug vaccination. Credit: Scripps Research Institute

Using a novel molecular analysis technique, scientists at The Scripps Research Institute (TSRI) have identified the chemical underpinnings of Captagon, also known as fenethylline, an illegal amphetamine-type

stimulant that has been linked to substance abuse and 'pharmacoterrorism' in the Middle East.

The study, published in the journal *Nature*, also identified a potential vaccine candidate that counteracted Captagon's effects in mouse studies.

"Our study illuminates not only why, but how Captagon, a presumed prodrug to amphetamine is being abused so heavily. It contains a component theophylline, which greatly enhances amphetamine's psychoactive properties, this discovery also provides a path for combating Captagon's abuse," said lead scientist Kim Janda, the Ely R. Callaway Jr. Professor of Chemistry and member of the Skaggs Institute for Chemical Biology at TSRI. The finding builds upon Janda's earlier research on the development of vaccines for drugs of abuse. In June, his anti-heroin vaccine passed a pivotal stage of preclinical testing.

Janda said he decided to explore Captagon due to its growing use in the Middle East. In recent years, Captagon has made headlines around the world due to its reported use as a performance-enhancing stimulant by ISIS fighters. The drug is said to be a source of "pharmacological morale" making fighters more alert, focused and resistant to fatigue. It has also gained notoriety for causing substance abuse issues among young people in the Middle East. In addition, production and global trafficking of counterfeit Captagon tablets from Syria has been implicated as a source of revenue for militant groups.

While the use of amphetamines to energize soldiers is not new, the researchers wondered why Captagon, in particular, was gaining popularity. "The Germans used amphetamines in World War II to help their soldiers stay up for long periods. Amphetamines have also been used in other conflicts," said Janda. "So we wondered why Captagon was being used in the Middle East instead of typical amphetamines which are easier to synthesize."

The researchers set out to explore the chemical interactions producing Captagon's effects. "This is drug that has been around for a long time," said the study's first author Cody Wenthur, a postdoctoral researcher in Janda's laboratory, noting at one time it was used therapeutically but became illegal in the U.S. and most countries in the 1980s. However, its mechanisms of action have long been poorly understood and debated in the scientific community.

"There was confusion about which chemical was actually responsible for its activity," said Wenthur. Captagon is composed of a combination of an amphetamine and theophylline, the latter occasionally used as an asthma drug. "The question was, 'does Captagon act on its own, or rather by breaking down into the two other drugs, and if so, is the amphetamine causing its action, is the theophylline causing its action, or both?'"

To address this question, Janda and Wenthur developed a new approach, called 'dissection through vaccination' or DISSECTIV, which enabled them to selectively explore Captagon's chemical properties as well as to determine a way to stop its onset. The study builds upon Janda's earlier work toward developing an anti-heroin vaccine, which blocks the "high" of heroin by neutralizing heroin's key psychoactive metabolites prior to reaching the brain. The vaccine was proven effective in non-human primates in a study published in June and is the first opioid vaccine against to pass this stage of preclinical testing.

"The strategy we came up with (DISSECTIV) uses vaccination as a biochemical tool," said Wenthur. "Basically, we take apart this complex compound into its pieces and then vaccinate against each piece individually to figure out which ones are activating the drug's key activities." The vaccinations cause the immune system to produce antibodies that block the action of each component one at a time, thus allowing the researchers to understand their functions through a process of elimination.

The researchers key findings were that when Captagon breaks down into amphetamine and theophylline separately when metabolized, the two drugs act synergistically and individually hit their targets at the same time. "It boosts the overall stimulant activity," said Wenthur. "You get a faster onset than other amphetamine drugs and a stronger effect than just amphetamine alone."

Based on this information, the researchers also developed a Captagon vaccine candidate and tested it in mice, where it neutralized most of the drug's behavioral effects. Further testing is planned.

Wenthur noted that the DISSECTIV approach also holds promise for better understanding other drugs which act on the brain, including natural products and medicines like antidepressants, anti-seizure drugs and antipsychotics. "When processed by the body, many of these compounds ultimately have multiple targets," he explained. "They don't just work by targeting one specific regulator of a single neurotransmitter like dopamine or serotonin, but often they'll work on a constellation of targets. This is a known problem in neuropharmacology. It has been very challenging to figure out which combination of targets is important for producing the desired effects and which are unhelpful and may be causing side effects."

He said their method provides researchers with a new way to understand such drug compounds, especially where individual components or metabolites interact to produce the complete effects of psychoactive species.

In addition to Janda and Wenthur, the other author of the study, "Vaccine-driven pharmacodynamic dissection and mitigation of Captagon psychoactivity," was Bin Zhou of TSRI.

More information: Cody J. Wenthur et al. Vaccine-driven

pharmacodynamic dissection and mitigation of fenethylline psychoactivity, *Nature* (2017). DOI: 10.1038/nature23464

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