An off-switch for drugs' toxic side effects

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Professor Alexandros Makriyannis and his team in the Center for Drug Discovery at Northestern have developed a series of drug compounds that are programmed to break down at a specific time. Credit: Mary Knox Merrill

When medications linger in the human body, they sometimes produce toxic side effects.

Professor Alexandros Makriyannis, the George D. Behrakis Trustee Chair in Pharmaceutical Biotechnology and Director of the Center for Drug Discovery at Northeastern, explained that many things can happen

to a drug inside our bodies once it is ingested. For instance, the drug can be modified into other byproducts with their own undesirable and unpredictable effects. Or it can remain embedded in the body's fatty tissues and then be slowly released into the circulatory system.

"If you had a way of controlling how long this drug sits in the body," Makriyannis said, "that would be a beneficial effect. It would be a safer drug."

In research recently published in the *Journal of Medicinal Chemistry* and *Medicinal Chemistry Letters*, Makriyannis and his team present not just one such drug but a whole series of them. "We call this concept controlled deactivation," he explained.

In this research, Makriyannis' team presents more than 100 compounds that are variants of drugs the researchers previously patented. These new drugs target the endocannabinoid system, which includes receptors within the surface of cells throughout our bodies that are responsible for functions like pain, mood, memory, and appetite modulation.

The original versions of the new drugs bind to the cannabinoid receptors—which were initially named for their recognition of the tetrahydrocannabinol molecule found in marijuana—and produce some effects such as increased appetite or a sense of euphoria. However, the development of these drugs has been limited by the negative side effects they elicit. In one high-profile case, a cannabinoid antagonist called Acomplia was designed to produce the opposite effects of cannabis. The drug was intended to treat obesity, but was pulled from the market when it was linked to increased suicide rates.

"Our lab works to design and make safer drugs with more controllable action," Makriyannis said. So with funding from the National Institute on Drug Abuse, he and his team set out to develop drugs that feature a

timing mechanism that would allow the drug to be deactivated as soon as it has performed its function and be transformed to inactive products.

This timing mechanism, Makriyannis said, is relatively simple—it just takes some very smart and specific chemistry.

The new drugs are chemically modified to be biodegradable and susceptible to particular enzymes in the blood. The enzymes would recognize these drug's new chemical features and "chew them up" right at that spot. The time it takes for the enzymes to finish their action can be controlled, and the resulting byproducts from this enzymatic activity are completely safe, according to Makriyannis.

Additionally, the drugs' chemical modifications ensure they don't stick around in the body's fatty tissues as long, and are thus expelled much more quickly.

"When we started making these new compounds, we weren't sure if they would be successful," Makriyannis said. "But actually, they worked even better than we'd hoped." Not only do the compounds have fewer side effects than the original versions of the drugs, they are also more potent and effective.

While the drugs in the present research all target receptors in the endocannabinoid system, the approach can be applied to virtually any small-molecule drug, Makriyannis said.

"We are controlling the fate of a drug by just designing these molecules in a manner that allows them to act predictably," he said. "It's a general concept that we've used to make analgesic compounds that are safer and very potent, but the same concept could be used to make neuroprotective drugs or other therapeutic agents."

More information: "Controlled-Deactivation Cannabinergic Ligands." Rishi Sharma, Spyros P. Nikas, Carol A. Paronis, JodiAnne T. Wood, Aneetha Halikhedkar, Jason Jianxin Guo, Ganesh A. Thakur, Shashank Kulkarni, Othman Benchama, Jimit Girish Raghav, Roger S. Gifford, Torbjörn U. C. Järbe, Jack Bergman, and Alexandros Makriyannis. *Journal of Medicinal Chemistry* 2013 56 (24), 10142-10157. DOI: 10.1021/jm4016075

The report titled "C-Ring Cannabinoid Lactones: A Novel Cannabinergic Chemotype" is available online: pubs.acs.org/doi/pdf/10.1021/ml4005304

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