Researchers develop new chemistry to make smart drugs smarter

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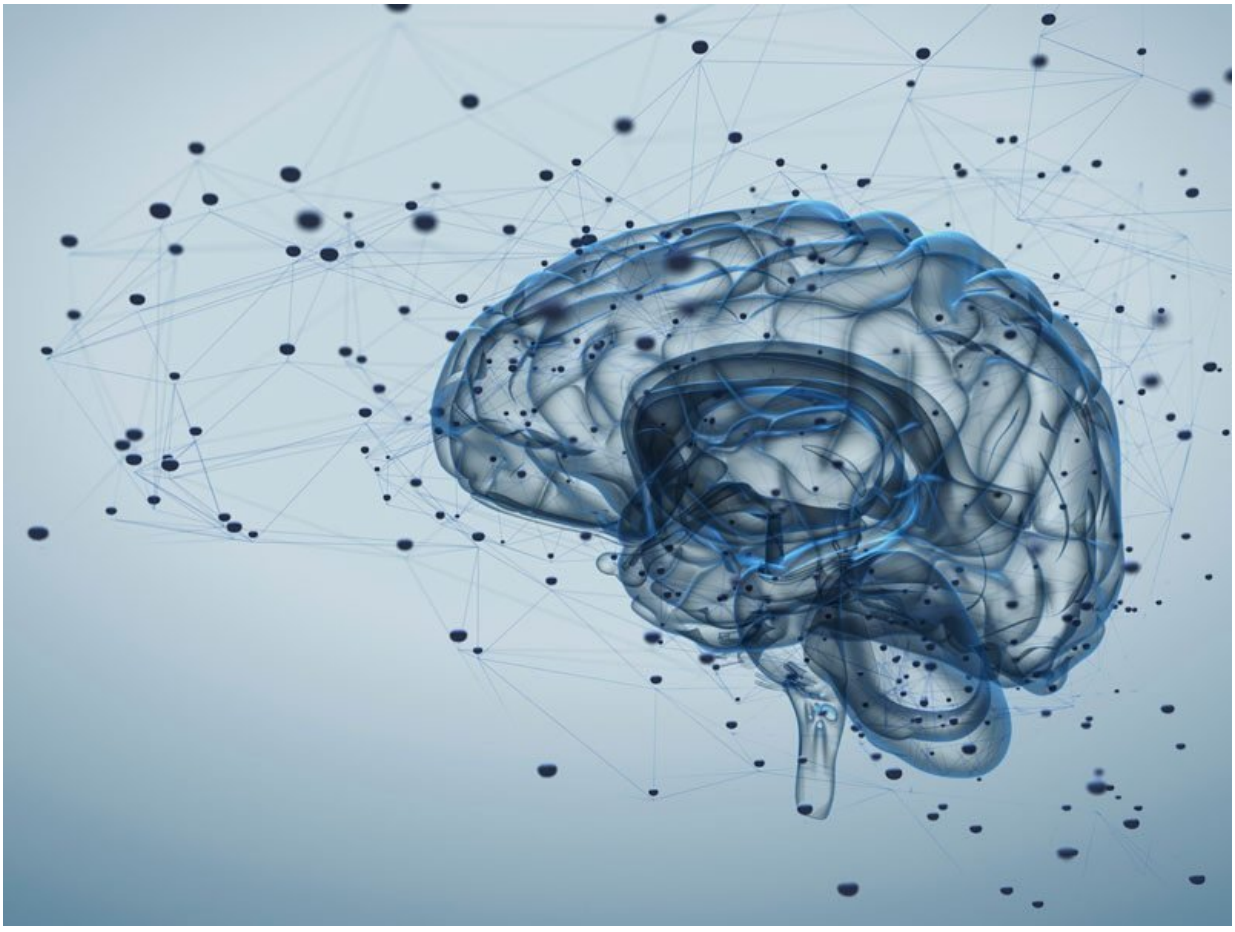

Credit: Georgia State University

A method to activate targeted drugs, or smart drugs, only at the selected

site of action, an approach that improves the drug's therapeutic effect and minimizes side effects, has been developed in a study led by Georgia State University.

Smart drugs, developed to improve the delivery problems of pharmaceutical drugs, are like guided missiles with warheads. They need a targeting molecule to guide pharmaceutical drug molecules to the desired site of action and a trigger to "drop the bomb" or release or activate the drug. In chemistry terms, such smart drugs are conjugates, or links, between a targeting molecule and a drug molecule.

For the most part, the issue of guiding and enriching such smart drugs to the desired site of action has been resolved. An example is the use of antibody-drug conjugates, an emerging class of cancer treatment that targets the delivery of drugs to cancer cells. However, the issue of when and how to trigger drug release, particularly at a sufficiently high concentration, has been a challenging task.

This study introduces new chemistry and a new concept to allow for "enrichment-triggered activation" of the drug molecule after delivering the smart drug to the desired site of action. The study tested doxorubicin, an anti-cancer drug, and carbon monoxide, an anti-inflammatory agent, using this delivery method and found the targeted approach effectively treated diseases such as acute liver injury in mice and cancer in cell culture. The researchers linked the active drug to a targeting molecule and then triggered the release of the drug at the desired site of action. The findings are published in the journal *Nature Chemistry*.

"The general idea is we have a targeting molecule that is conjugated to a payload (pharmaceutical drug molecule), and in between, there's a linker," said Dr. Binghe Wang, Regents' Professor of Chemistry and director of the Center for Diagnostics & Therapeutics at Georgia State, a Georgia Research Alliance Eminent Scholar in Drug Discovery and a

Georgia Cancer Coalition Distinguished Cancer Scholar. "The entire purpose of this is to enrich drug concentration at the site of action. This allows a higher concentration of the drug at the site of action, but minimizes the concentration elsewhere. Essentially, it's almost like a guided missile.

"What we have developed is an approach called enrichment-triggered prodrug activation. Most other chemical approaches rely on some kind of linker chemistry that is not specific enough or there's a premature release in the general circulation. What we have essentially is a way to control release once the concentration of the drug reaches a certain level. Let's say you have someone who has prostate cancer. If the drug concentration at the prostate can be a hundredfold higher than the concentration in the bloodstream, chances are you can probably kill all the cancer cells without causing all these side effects."

In this study, the researchers used this targeted drug delivery approach to administer carbon monoxide to mice and treat acute liver injury. They saw a very potent effect, maybe 10 to 30 times more effective than traditional drug delivery, Wang said. They also tested the anti-cancer drug doxorubicin in cell culture.

They found it's necessary to use a very stable linker to connect the targeted molecule and active drug so the linker can remain steady as it circulates in the bloodstream. They also needed to trigger a mechanism to release the drug at a desired site of action.

"The linker chemistry design has been very tricky," Wang said. "There's a lot of effort that went into it. What we have is something very unique in the sense that we have designed an approach that is not based on typical chemistry. When the (drug) concentration reaches a certain level, then it will automatically start releasing very quickly."

While this study's targeted drug delivery approach resembles that of antibody-drug conjugates, which target an antibody (a protein that recognizes foreign substances) on the surface of cancer cells, the current approach doesn't require having antibodies.

"There are many other molecules that one can use to target different kinds of tissues, diseased organs or sites," Wang said.

This approach is also not limited to the cell surface, as used in antibody-drug conjugate delivery, because small molecules are used for targeting and cleaving the drug from the targeting molecule.

More information: Yueqin Zheng et al. Enrichment-triggered prodrug activation demonstrated through mitochondria-targeted delivery of doxorubicin and carbon monoxide, *Nature Chemistry* (2018). DOI: 10.1038/s41557-018-0055-2

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