Light-activated molecular machines get cells 'talking'

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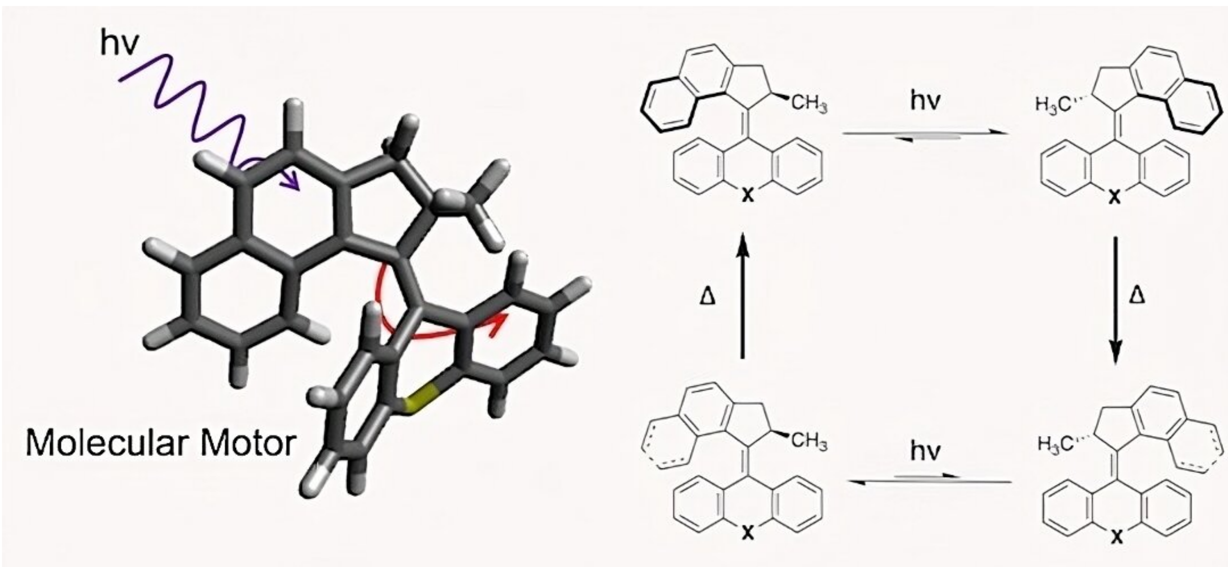

Model of a molecular motor (left) and its rotation cycle. (Image courtesy of the Tour lab/Rice University). Credit: Rice University

One of the main ways cells "talk" to each other to coordinate essential biological activities such as muscle contraction, hormone release, neuronal firing, digestion and immune activation is through calcium signaling.

Rice University scientists have used light-activated molecular machines to trigger intercellular calcium wave signals, revealing a powerful new strategy for controlling cellular activity, according to a new study published in *Nature Nanotechnology*. This technology could lead to improved treatments for people with heart problems, digestive issues and more.

"Most of the drugs developed up to this point use chemical binding forces to drive a specific signaling cascade in the body," said Jacob Beckham, a chemistry graduate student and lead author on the study. "This is the first demonstration that, instead of chemical force, you can use mechanical force—induced, in this case, by single-molecule nanomachines—to do the same thing, which opens up a whole new chapter in drug design."

Scientists used small-molecule-based actuators that rotate when stimulated by visible light to induce a calcium-signaling response in smooth muscle cells.

We lack conscious control over many of the critical muscles in our body: The heart is an involuntary muscle, and there is smooth muscle tissue lining our veins and arteries, controlling blood pressure and circulation; smooth muscle lines our lungs and intestines and is involved in digestion and breathing. The ability to intervene in these processes with a molecular-level mechanical stimulus could be game-changing.

"Beckham has shown that we can control, for example, cells' signaling in a heart muscle, which is really interesting," said James Tour, Rice's T. T. and W. F. Chao Professor of Chemistry and a professor of materials science and nanoengineering.

"If you stimulate just one cell in the heart, it will propagate the signal to the neighboring cells, which means you could have targeted, adjustable molecular control over heart function and possibly alleviate arrhythmias," Tour said.

Activated by quarter-second-long light pulses, the molecular machines allowed scientists to control calcium signaling in a cardiac myocyte cell culture, causing the inactive cells to fire.

"The molecules essentially served as nano-defibrillators, getting these heart muscle cells to start beating," Beckham said.

The ability to control cell-to-cell communication in muscle tissue could be useful for the treatment of a wide range of diseases characterized by calcium-signaling dysfunction.

"A lot of people who are paralyzed have huge digestive problems," Tour said. "It would be a big deal if you could alleviate these issues by causing those relevant muscles to fire without any kind of chemical intervention."

The molecule-sized devices activated the same calcium-based cellular signaling mechanism in a live organism, causing whole-body contraction in a fresh-water polyp, or Hydra vulgaris.

"This is the first example of taking a molecular machine and using it to control an entire functioning organism," Tour said.

Cellular response varied based on the type and intensity of the mechanical stimulation: Fast, unidirectionally rotating molecular machines elicited intercellular calcium wave signals, while slower speeds and multidirectional rotation did not.

Moreover, adjusting the intensity of the light allowed scientists to control the strength of the cellular response.

"This is mechanical action at the molecular scale," Tour said. "These molecules spin at 3 million rotations per second, and because we can adjust the duration and intensity of the light stimulus, we have precise spatiotemporal control over this very prevalent cellular mechanism."

The Tour lab has shown in previous research that light-activated molecular machines can be deployed against antibiotic-resistant infectious bacteria, cancer cells and pathogenic fungi.

"This work expands the capabilities of these molecular machines in a different direction," Beckham said. "What I love about our lab is that we are fearless when it comes to being creative and pursuing projects in ambitious new directions."

"We're currently working towards developing machines activated by light with a better depth of penetration to really actualize the potential of this research. We are also looking to get a better understanding of molecular-scale actuation of biological processes."

More information: Beckham, J.L. et al. Molecular machines stimulate intercellular calcium waves and cause muscle contraction, *Nature Nanotechnology* (2023). doi.org/10.1038/s41565-023-01436-w. www.nature.com/articles/s41565-023-01436-w

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