Exploring heart beats with light

Researchers can genetically engineer mouse and zebrafish heart muscles to respond to light, according to two recently published studies. To carry out these studies, the research teams applied the technique of optogenetics, which uses proteins called channelrhodopsin and halorhodopsin. These proteins, which are taken from microorganisms, are light-activated ion channels. By expressing these proteins in neurons, scientists have previously used light to control the activity of individual neurons and of brain circuits in animals.

Both neurons and heart muscle cells are activated by electrical action potentials. An influx of ions into activated voltage-gated ion channels that lie in the plasma membranes of these cells generates these action potentials. To electrically stimulate heart muscle cells in the lab, scientists typically apply an external electric field to locally induce action potentials. But this approach produces toxic gases and can only be used for short durations, thereby limiting its utility.

To try to overcome such limitations, Philipp Sasse and colleagues from the University of Bonn in Germany decided to use the channelrhodopsin protein (*Nat. Methods* **7**, 897–900; 2010). They generated a transgenic mouse stem cell line that expressed channelrhodopsin, which produces action potentials when exposed to blue light. The team then converted these channelrhodopsin-expressing stem cells into heart muscle cells. They exposed a group of these cells to blue light, which caused the cells to start beating in unison. Shining blue light on a sub-group of heart cells that were already beating caused the sub-group to start beating out of sync.

Maxim Borovkov

Sasse and colleagues then generated transgenic mice from the channelrhodopsin-expressing embryonic stem cells. To analyze the effect of channelrhodopsin activation *in vivo*, the researchers intubated and ventilated the channelrhodopsin-expressing mice, used a microscope to shine blue light onto the beating hearts of these mice and recorded electrocardiogram measurements from these mice. They were able to use light pulses as short as 1 millisecond to stimulate the hearts of these mice.

Another research group generated transgenic zebrafish that expressed both channelrhodopsin and halorhodopsin (which, when exposed to orange light, silences beating heart cells). Didier Stainier of the University of California, San Francisco and colleagues were able to use optical tools to find 'pacemaker' cells and to simulate tachycardia, bradycardia, atrioventricular blocks and cardiac arrest in these zebrafish (*Science* **330**, 971–974; 2010). These optogenetic techniques could be used to improve understanding of embryonic heart development and to develop better heart attacks models.

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BISPHENOL-A MAY COMPROMISE FERTILITY

Bisphenol-A (BPA) is a chemical present in materials many people use every day, such as polycarbonate plastics and the inner coatings of food and beverage containers. Exposure to BPA is quite pervasive: the chemical has been detected in the urine of more than 92% of those in the US who have been tested, and levels are typically higher in children and adolescents than in adults. In the body, BPA acts like the natural hormone estrogen and hence can have hormone-related effects. Rodents exposed to BPA during fetal and neonatal development had an increased risk of mammary and prostate cancers, altered behavior and obesity.

Because of its ubiquity and potential health effects, BPA has come under increasing scrutiny. In one recent study, a group of scientists at Tufts University School of Medicine (Boston, MA) evaluated the effects of intra-uterine and perinatal exposure to BPA on reproductive capacity of female mouse pups.

The group found that fertility decreased over time in female CD-1 mice that were exposed to BPA during fetal and neonatal development (*Environ. Health Perspect.* doi:10.1289/ehp.1002559; published online 2 December 2010). These mice had fewer successful pregnancies and delivered fewer pups overall than did mice that were not exposed to BPA. Notably, this effect was not apparent in the mice's first pregnancies, but became obvious with later pregnancies. "This finding is important because standard tests of reproductive toxicology currently consist of assessing the success of a first pregnancy in young animals," said Beverly S. Rubin, one of the study leaders, in a press release. "If subsequent pregnancies are not examined, relevant effects may be missed."

The effects of BPA were comparable with those of diethylstilbestrol (DES), a hormonally active chemical known to cause reproductive impairment in women after fetal exposure. Like BPA, DES (when tested at low doses) did not cause obvious reproductive problems during first pregnancies, as assessed by the standard tests used by regulatory agencies to evaluate toxicity.

The researchers tested three different doses of BPA, all of which are within the range to which humans are known to be exposed and are below the maximum acceptable daily dose determined by the Environmental Protection Agency. They found that the effects of BPA were dose-specific: the lowest and highest doses both affected fertility but the intermediate dose did not. Carlos Sonnenschein, also a study leader, pointed out that "chemicals have to be tested at a variety of doses in order to avoid false 'no effect' results."

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