

When Sperm Give Up Their Secrets

A new window on sperm cells' ion channels could ultimately help control populations, human and otherwise.

FEW BIOLOGICAL IMAGES HAVE WORKED THEIR WAY INTO THE POPULAR IMAGINATION more successfully than the sperm cell. You needn't have ever opened a science textbook to recognize that formidable little swimmer propelled by a tadpole-like tail. ¶ But until recently, imagination (as opposed to genuine knowledge) was all scientists could bring to bear on the understanding of spermatozoa, because the intimate details of their lives were hidden within "ion channels"—networks of pore-forming proteins that help regulate the cells' electrochemical activity. While standard laboratory techniques used to eavesdrop on ion-channel functioning have worked fine for most other types of cells, sperm cells proved



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resistant—until a research team led by HHMI investigator David E. Clapham, a neurobiologist at Harvard Medical School, found a way around the problem.

In 2001, Clapham discovered a particular ion channel, which he named CatSper1, unique to the sperm's tail. This channel appeared to be necessary for the sperm to enter into "hyperactivation," the process that enables it to penetrate the egg.

Young, immature sperm cells tend to swim in an orderly, highly symmetrical pattern. But as they travel farther into the vaginal canal and enter the alkaline environment housing the egg, their pattern changes. As hyperactivation begins, the sperm's swimming pattern becomes less symmetrical. The tail assumes a whip-like motion, enabling it to strike the egg's surface with greater force. When Clapham "knocked out"—that is, inactivated—the gene for CatSper1 in mouse sperm cells, 100 percent of the mice became infertile.

Normally, when researchers want a closer look at an ion channel of interest,

they use a technique called patch-clamp recording. In this routine procedure, an electrode provides a window through the membrane into the cell's machinations. In addition, researchers can introduce various chemicals and substrates through the probe to manipulate and study the cell's properties.

"We tried this [patch-clamp] technique over a thousand times with sperm cells, and failed at every attempt," says Clapham. "We found that sperm cells aren't amenable to it." This may result, at least in part, from their rigid membrane and constant wriggling.

Eventually, Yuriy Kirichok, a postdoctoral fellow in Clapham's lab, discovered that the sperm's cytoplasmic droplet, a remnant of the precursor germ cell cytoplasm, was the ideal entry point for the patch-clamp probe, providing a way around sperm's tough skin and unruly movements. Then, Clapham and his team found that CatSper1 enables calcium to enter into the sperm, which changes the swimming pattern into the whip-like motion needed for penetrating the egg. "This has opened up a whole new pathway for probing these electrical currents and finding out exactly what they do," says Clapham. "I feel like we've discovered the entrance into an ancient pyramid that no one has ever been inside of before."



Illustration: Jeffrey Decoster Photo: UT Southwestern News & Publications

The researchers published their findings in the February 9, 2006, issue of *Nature*.

At roughly the same time that Clapham identified CatSper1, David L. Garbers, an HHMI investigator at the University of Texas Southwestern Medical Center at Dallas, discovered two other sperm-specific proteins that affect fertility: CatSper2 and sNHE. Mice in which CatSper2 was knocked out had much the same profile as Clapham's CatSper1 knock-outs—that is, they were unable to achieve a hyperactivated state. In sNHE knock-outs, by contrast, the sperm were unable to swim at all.

"These findings have changed our whole outlook on fertility," says Garbers, who authored a review paper on CatSper and sNHE in the May 16, 2006, issue of *Molecular and Cellular Endocrinology*. "We used to think that as long as sperm can move,

the male is fertile. Now, with these CatSper studies, we're seeing that motility isn't enough. Sperm cells need hypermotility."

Both Clapham and Garbers are involved with the biotech company Hydra Biosciences, Inc., in Cambridge, Massachusetts (Clapham as cofounder, Garbers as scientific advisor). The company is seeking to translate these CatSper findings into a male contraceptive pill.

"CatSper proteins are unique to the sperm cell," says Clapham. "So theoretically, a pill that targets and disables a CatSper protein should have no adverse side effects

whatsoever. And because such a drug wouldn't work by affecting hormone levels, it would only be taken as needed."

Garbers, however, is thinking beyond simply adding to the armamentarium of human contraceptives. He also sees these findings as a potential way to control certain animal populations.

"Because fertilization is species-specific," he says, "in theory we could make drugs that target just one kind of animal. You could set up rodent baits that do nothing other than render the rodents who eat it infertile. Similarly for the deer population."

And if, for some reason, the CatSper proteins don't work as targets, there are a lot of other candidates. "Sperm cells contain somewhere between 1,000 and 2,000 unique proteins," says Garbers. "And for a male contraceptive, that's perfect. There will no doubt be many, many targets from which to choose." ■ —DAVID CAMERON

David Garbers passed away on September 5. A remembrance can be found on page 57.

FOR MORE INFORMATION: For more about how the body exploits ion channels, visit the [Online Bulletin](#).



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