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## How Sperm Crack the Whip

Researchers have identified a key component of the mechanism spermatozoa use to abruptly convert their tail motion from a steady swimming undulation to the whip-cracking snap that thrusts them into an egg. The finding opens a new research pathway that the researchers said could help scientists both recognize new forms of male infertility and design new contraceptives to thwart sperm entry into the egg.

What's more, they said, the exquisitely delicate analytical technique they used to eavesdrop on the electrical currents inside the squirming sperm cell could literally open a new window into its largely mysterious inner workings.

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Howard Hughes Medical Institute investigator David E. Clapham and his colleagues published their findings in the February 9, 2006, issue of the journal *Nature*. Lead author on the paper was Yuriy Kirichok and the other co-author was Betsy Navarro, both in Clapham's laboratory at Harvard Medical School.

According to Clapham, it has long been known that a spermatozoa's arrival in the alkaline environment of the female reproductive tract triggers its tail's whiplike motion, called hyperactivation. In 2001, the researchers showed that a protein called CatSper1, found only in the sperm tail, was required for male fertility. Subsequently, with colleagues at the University of Washington and at the University of Texas Southwestern, CatSper was found to be required for hyperactivation. CatSper proteins are components of pores in the sperm cell membrane called ion channels. In an alkaline environment, these pores open and allow calcium to enter the cell.

In earlier experiments, the researchers had attempted to study the CatSper ion channel with a technique called patch clamp recording. In this widely used method of studying electrical activity in cells, a tiny hollow pipette is snugged tightly against the cell membrane. With gentle suction, the

membrane is delicately ruptured, opening a window into the cell that allows measurement of its electrical properties, as well as introduction of chemicals to perturb those properties for study.

However, said Clapham, the constant wriggling of spermatozoa, as well as the way their tough membranes stretch tightly over underlying structures, made the cells incompatible with this research technique.

Back in 2001, we made more than a thousand attempts to patch clamp sperm without success, said Clapham. We had been quite frustrated by it. However, Yuriy finally discovered a way to patch clamp the cells, which was central to the success reported in this paper. Basically, Kirichok found that he could patch clamp the pipette into a microscopic cytoplasmic droplet that is present in sperm before ejaculation, but is usually lost in mature sperm.

Patch clamp studies on spermatozoa with remnant cytoplasmic droplets revealed that CatSper1 was a major component of the calcium ion channel responsible for alkaline-activated hyperactivation and male fertility.

According to Clapham, the finding represents the beginning of an important new research pathway. It's like opening a chamber in an ancient pyramid, because no one had ever seen inside sperm cells to measure all the currents that control their activity, he said. We are already measuring many of these currents and beginning to answer questions about what they are and what they do.

Further studies, said Clapham, will aim at exploring the many controlling currents inside sperm and also tracing how calcium triggers hyperactivation once it enters the cell. Such studies will enable exploration of sperm machinery from tail to head - analyzing processes ranging from tail motility to the mechanism by which the sperm head delivers its genetic payload to the egg, he said.

Such research could yield insight into some male infertility, said Clapham. Still-unidentified mutations in any of the four CatSper proteins - all of which are involved in motility - could underlie some forms of infertility, he said.

Also, these proteins are good targets for contraception, he said. We know that defects in CatSper1 block fertilization in mice. And since the channels in human sperm are very similar, there's no reason to believe you couldn't develop a male or female birth control pill that would block the protein before it functions to hyperactivate sperm, preventing fertilization, he said.