Scientists identify genetic switch for female sexual behavior

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The key to successful sexual reproduction can be traced to a single receptor in the brain, according to a new study by Stanford scientists.

The research, which was published in *Current Biology*, was conducted in fish, but the receptor responsible is present in all animals and has implications for understanding social behavior.

The African cichlid fish, A. burtoni, reproduces during an elaborate mating routine. A male fish attracts a fertile female by rapidly quivering his brightly colored body. If she chooses him, he guides her back to his territory, where he quivers some more as she pecks at fish egg–colored spots on his anal fin. Next, she lays eggs and quickly scoops them up in her mouth.

With a mouthful of eggs, she continues pecking at the male's spots, "believing" them to be eggs to be collected. As she does, he releases sperm from near his anal fin, which she also gathers. This fertilizes the eggs, and she carries the embryos in her mouth for two weeks as they develop.

All this works, however, only if it's timed exactly to the female's ovulation schedule.

"How is it that these females can time their reproduction to coincide when they are fertile?" said Russell Fernald, the Benjamin Scott Crocker Professor of Human Biology at Stanford and senior author on the study. "They will not approach or choose males until they are ready to reproduce, so there must be something in their brains that signals when sexual behavior will be important."

The scientists began by considering signaling molecules previously associated with sexual behavior and reproduction, and eventually settled on a molecule called PGF2α. They found that by injecting it into the female fish, they would engage in mating behavior even if they were non-fertile, doing the quiver dance with males, but wouldn't actually lay eggs since they had none.

The scientists keyed in on a receptor for PGF2α in the preoptic area (POA) within the hypothalamus of the brain, a region involved in sexual behavior across animals. They suspected that when PGF2α levels elevate

in the fish, the molecule attaches to this receptor and triggers sexual behavior.

To test this, lead author Scott Juntti and colleagues used the CRISPR/Cas9 gene-editing system to delete the receptor gene of female fish embryos, so that the receptor couldn't be activated by PGF2α. "CRISPR/Cas9 is revolutionizing biology," said Juntti, who is a research associate in Fernald's lab. "In principle, we can now test the function of specific genes in any organism we study."

They raised these mutant fish among normal fish, and at sexual maturation observed their mating behavior. The mutant fish showed a dramatic change in their behavior: In contrast to naturally mating females and non-fertile fish injected with PGF2α, mutant females did not perform the quiver dance or lay eggs. Fernald said that this implicates the role of the PGF2α receptor as clearly having a starring role in reproduction.

"We think that we have found the key genetic component that regulates reproduction in a certain way," Fernald said. "It influences behavior, but more importantly it influences the actual act of laying eggs."

The next steps for this work will involve understanding other behaviors that are regulated by this receptor, and the finding provides insight into both the evolution of reproduction and sexual behaviors.

In mammals and other vertebrates, PGF2α promotes the onset of labor and motherly behaviors, and the new research, coupled with other studies, suggests that PGF2α signaling has a common ancestral function associated with birth and its related behaviors.

"Now that we've identified this receptor," Juntti said, "we can get a handle on other components of the brain circuits that control social

behavior, and investigate how they've evolved."

More information: Scott A. Juntti et al. A Neural Basis for Control of Cichlid Female Reproductive Behavior by Prostaglandin F2α, *Current Biology* (2016). DOI: 10.1016/j.cub.2016.01.067

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