Fish courtship pheromone uses the brain's smell pathway

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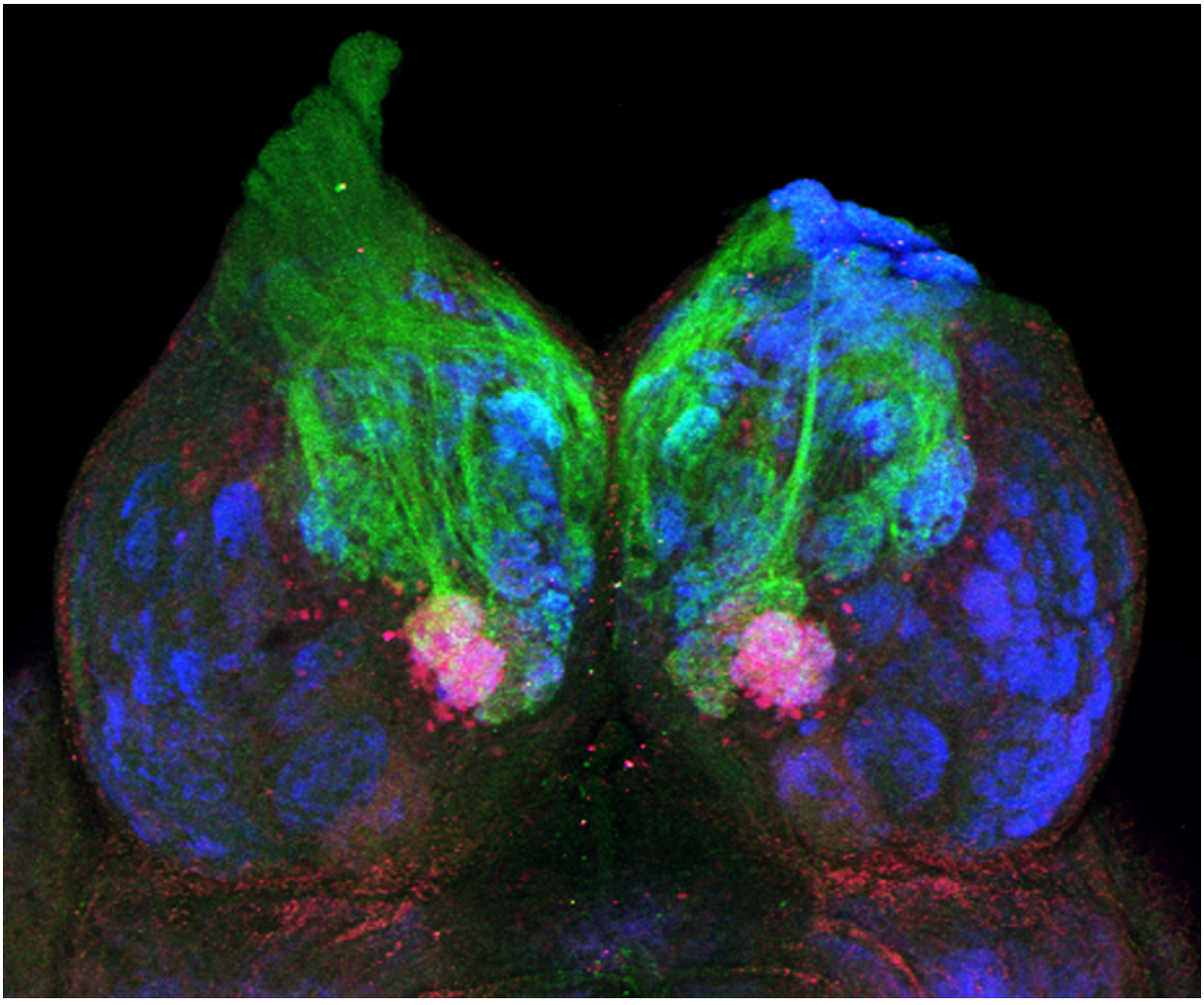


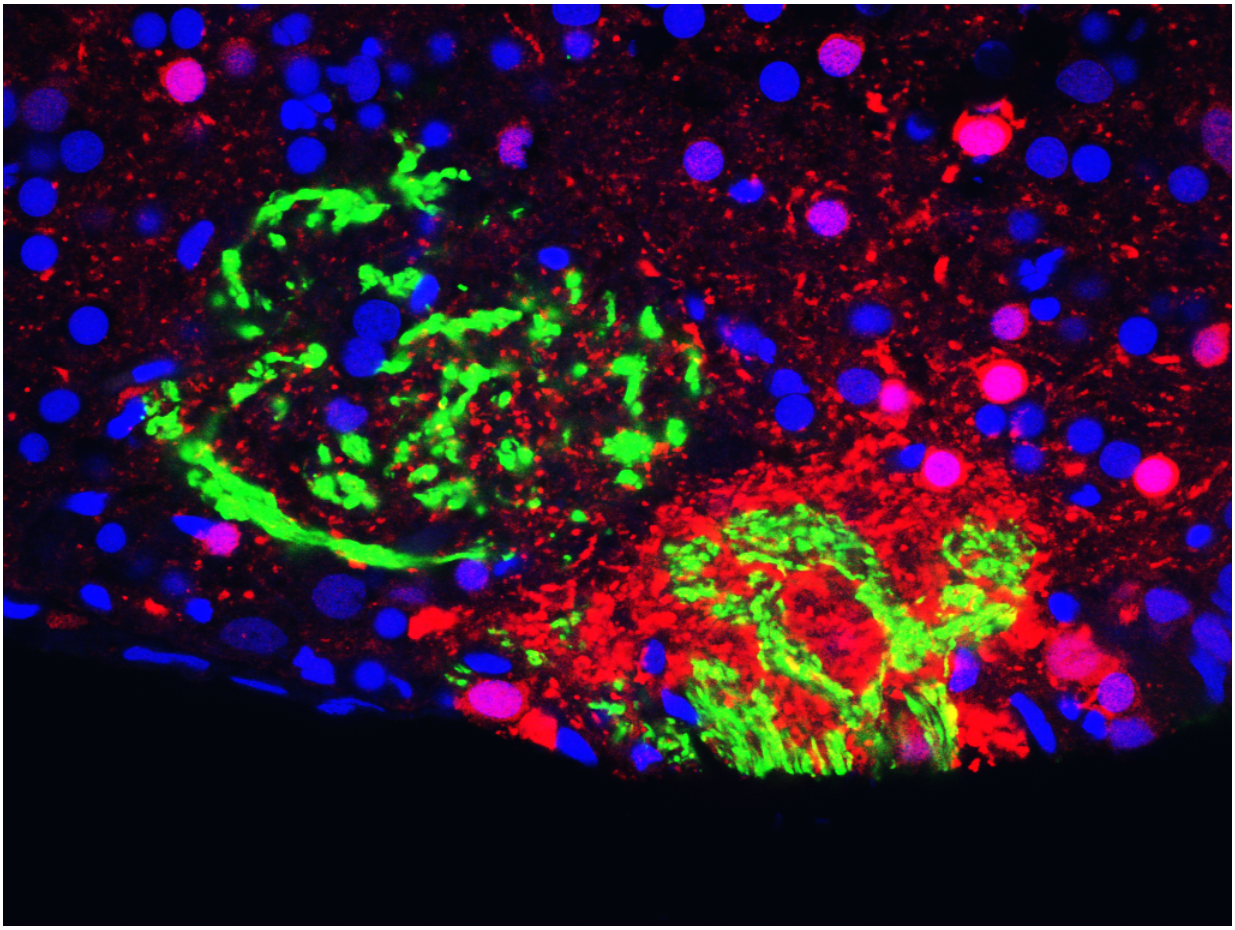
$PGF2_{\alpha}$ activates two ventromedial glomeruli in the zebrafish olfactory bulb, as revealed by neural activation marker (pERK: red). Green: GFP-expressing olfactory axons, blue: glomerular structure visualized with anti-SV2 antibody. Credit: RIKEN

Research at the RIKEN Brain Science Institute in Japan has revealed that a molecule involved in fish reproduction activates the brain via the nose. The pheromone is released by female zebrafish and sensed by smell receptors in the noses of the males. The neural pathway and brain areas involved in transforming this molecular messenger into courtship behavior in fish were also identified and reported in *Nature Neuroscience* on May 30.

Prostaglandin $F2_{\alpha}$ ($PGF2_{\alpha}$) is a reproductive hormone in female fish and mammals that is involved in ovulation and uterine contraction. In fish, it is also pheromone—a social and sexual signaling molecule used to attract the opposite sex—that is secreted by females in their urine. Males will normally swim toward even small concentrations of the molecule, but the researchers, led by Yoshihiro Yoshihara, found that male fish without a sense of smell were indifferent when $PGF2_{\alpha}$ was added to their tank.

$PGF2_{\alpha}$ synchronizes reproductive behaviors between female and male zebrafish, but how this happens was unknown. Having confirmed that sensory tissue responsible for smelling was needed for males to sense $PGF2_{\alpha}$, researchers then found that the only type of neurons activated by it are ciliated olfactory sensory neurons. The team then searched for the receptor within these neurons that detects $PGF2_{\alpha}$.

Contrary to expectations, the key players were not prostaglandin receptors. Molecular labeling revealed that $PGF2_{\alpha}$ only bound to two specific olfactory receptors. These olfactory receptors are evolutionarily quite different from prostaglandin receptors, and the same or corresponding olfactory receptor genes are present in other fish and mice, which indicates that a similar mechanism for reproductive communication might be present within other species.



$PGF2_{\alpha}$ activates a ventromedial glomerulus in the zebrafish olfactory bulb, as revealed by neural activation marker (pERK: red). A neighboring glomerulus is negative for pERK. Green: GFP-expressing olfactory axons, blue: DAPI staining. Credit: RIKEN

The researchers also found that through these olfactory receptors, $PGF2_{\alpha}$ activates a direct, dedicated neural pathway to the areas of the brain that are responsible for eliciting courtship behavior in male fish. The ciliated olfactory sensory neurons send their signals to specific regions called glomeruli in the olfactory bulb of the brain, which in turn relay them to distinct forebrain areas. This "labeled line", in which circuits only

transmit information about particular stimuli from a limited number of receptors, is also how the sense of taste functions. Hardwired pathways like this are common for innate behaviors, says Yoshihara, and it may have been an evolutionary accident that the $PGF2_{\alpha}$ molecule was well-matched to certain olfactory receptors, facilitating the use of the "smell pathway" for reproductive purposes.

Finally, the researchers tested the response to $PGF2_{\alpha}$ in male fish that were lacking the genes for one of the olfactory receptors they had identified. These fish weren't drawn to $PGF2_{\alpha}$ in their tank, spent less time chasing female fish, and were less successful at spawning. A smell receptor thus seems to be the gateway for $PGF2_{\alpha}$ into the male fish brain. Pheromone signaling works hand in hand with other senses like vision to bring about the courtship dance that increases a fish's chances of mating.

More information: Yabuki Y, Koide T, Miyasaka N, Wakisaka N, Masuda M, Ohkura M, Nakai J, Tsuge K, Tsuchiya S, Sugimoto Y, Yoshihara Y (2016) Olfactory receptor for prostaglandin F2α mediates male fish courtship behavior. *Nat Neurosci*. DOI: 10.1038/nn.4314

Provided by RIKEN