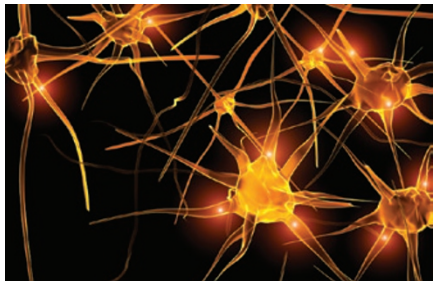
Estrogen helps make mice male

Sexual dimorphism is the presence of different behaviors and characteristics in males versus females. Its development relies on an intricate interplay of genetic, chromosomal and hormonal factors, particularly during certain stages of development. In mammals, sexual dimorphism is thought to result from exposure to sex hormones during the perinatal stage of development. In male rats, an increase in testosterone expression occurs during this period, resulting in male-specific brain circuitry and the establishment of certain male-specific characteristics. Now, a new study has identified the neural pathways underlying territorial behavior in male mice and, furthermore, shown that these pathways are controlled by estrogen.

Researchers had known that estrogen was involved in sexual dimorphism, but not how. The new work, done by Nirao Shah and colleagues at the University of California, San Francisco and Fujita Health University (Toyoake, Japan), elucidates a mechanism of action for estrogen in regulating male



Monika Wisniewska

territorial behavior. They found that male mice had a greater number of neurons that express an enzyme called aromatase in specific areas of the brain known to be involved in sexual and aggressive behaviors (*Cell* **139**, 61–72; 2009). These aromatase-expressing neurons also established a unique circuitry in male brains. Aromatase converts testosterone into estrogen, which is required for the unique circuitry.

When Shah's group exposed female pups to estrogen, the females began engaging in aggressive and territorial behaviors typically found in males, and the aromatase neurons in their brains took on the 'male' circuitry. Exposure to estrogen did not affect sexual behavior in the females, however. "This really changes the way we view male and female behaviors," said Shah. "What we previously looked upon as a single unit of gender-related behavior, we now see as a collection of separate behaviors controlled at least in part by distinct neural pathways."

The new results add to the body of evidence that estrogen signaling has a key role in the expression of male aggressive behavior and the development of the neural pathways that underlie it. Neural pathways in the brain are largely conserved between mice and humans, and hormone-induced dimorphism may also be conserved. But much more research is needed on the development of sex-specific neural pathways; many other factors, including genetics and socialization, contribute to sexual differentiation.

Shah's approach could also be used in studies attempting to link other specific behaviors with their underlying neural pathways.

Monica Harrington

GLOWING WORMS ELUCIDATE NEURONAL SIGNALING

To communicate with one another, neurons use chemicals that range from classical neurotransmitters, such as serotonin, to neuropeptides like beta-endorphin. Neurons use the protein-like neuropeptides to initiate and modulate complex behaviors.

Before being sent to other cells, neuropeptides must travel from the cell body of a neuron out to its axons. In the cell body, neuropeptide precursor proteins and their processing enzymes join together to form dense core vesicles (DCVs). These membrane-enclosed sacs then travel to the axons. Along the way, DCVs discard unneeded components and develop into dense packages of neuropeptides and other factors involved in synaptic signaling. Recent research in glowing worms helps explain how the maturation of DCVs is regulated.

Properly functioning DCVs are essential for neuronal signaling. *Caenorhabditis elegans* that are unable to secrete DCVs are severely paralyzed. To better understand the process of DCV transport and secretion, researchers led by Kenneth Miller (Oklahoma Medical Research Foundation, Oklahoma City) performed a genetic screen for DCV regulators. They found that the protein UNC-108 regulates DVCs (*J. Cell Biol.* **186**, 881–895; 2009). Specifically, some *unc-108* mutations suppressed movement in hyperactive mutant worms. UNC-108 is homologous to the human Rab2 protein, which is involved in trafficking intracellular membranes.

Miller's group then studied how these *unc-108* mutations affected DCV function. Stefan Eimer of the European Neuroscience Institute Göttingen (Germany) and colleagues also analyzed DCV movement in *unc-108* mutants (*J. Cell Biol.* **186**, 897–914; 2009). Both research groups found that the *unc-108* mutants had defects in DCV signaling. Surprisingly, however, these mutant worms had unimpaired processing and secretion of neuropeptides.

To further investigate the *unc-108* mutants, the research groups labeled neuropeptides in the DCVs with a fluorescent protein. They saw that mutant worms had decreased fluorescence in their axons, meaning the DCVs had discarded the fluorescent proteins before reaching the axons. Since the processing and secretion of neuropeptides had remained unchanged in the *unc-108* mutants, the researchers concluded that the mutant UNC-108 protein must have caused the DCVs to lose some other cargo that is essential to proper DCV functioning.

The research teams hope to determine which essential components of the DCVs become discarded in *unc-108* mutants. They also plan to explore potential mechanisms for how UNC-108 prevents the loss of this cargo in normally functioning worms, with the goal of learning more about the role of Rab2 in human neuron signaling.

Kirsten Dorans