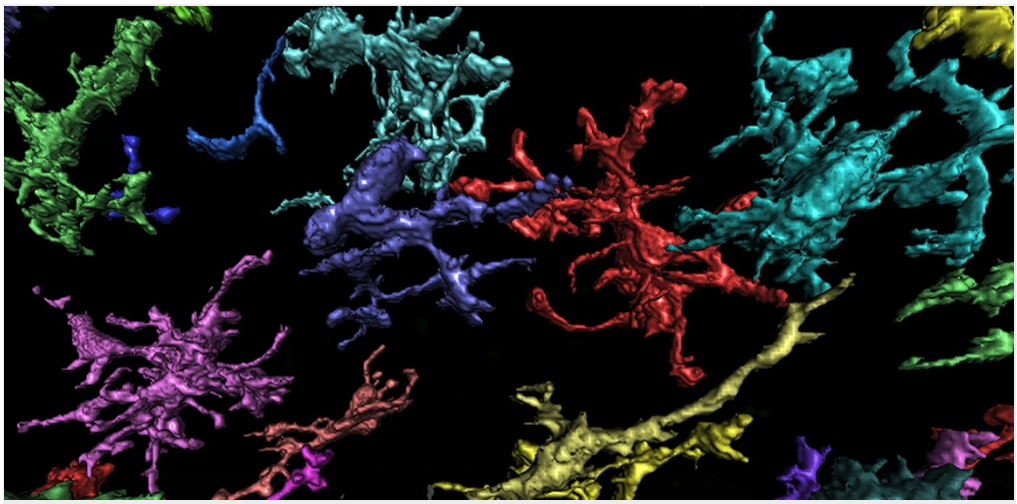
NATURE | NEWS

Sex divide seen in mechanism that produces persistent pain

Research showing that male and female mice regulate pain sensitivity differently raises questions about gender balance in experimental design.

Moheb Costandi

29 June 2015



Simon Beggs/Wellcome Images

Cells called microglia play a key role in regulating persistent pain in male mice.

Different immune cells regulate pain sensitization in male and female mice, according to research published on 29 June in *Nature Neuroscience*[1].

The surprising biological divide may explain why some clinical trials of pain drugs have failed, and highlights shortcomings in the way that many researchers design their experiments.

The immune system has important roles in chronic pain, with cells called microglia being key players. Microglia express a protein called brain-derived neurotrophic factor (BDNF) to signal to spinal-cord neurons. When injury or inflammation occurs, this signal sensitizes the body to pain, so that even light touch hurts.

Robert Sorge, a psychologist at the University of Alabama in Birmingham, and his colleagues induced persistent pain and inflammation in healthy male and female mice by severing two of the three sciatic nerve branches in their hind paws. Seven days later, they injected the animals with one of three drugs that inhibit microglial function.

They found that all three drugs reversed pain sensitization in the male animals, as had been previously reported. But the treatments had no effect on the females, even though the animals had displayed equivalent levels of pain.

The researchers also genetically engineered mice in which the BDNF gene could be deleted in microglia at any time during the animals' lives. At first, these animals exhibited normal responses to a nerve injury. Killing the microglia one week later extinguished that hypersensitivity in the male animals, but not in the females. This confirmed that in males, hypersensitivity to pain depends on BDNF signals from microglia, but that in females it is mediated by some other mechanism.

The importance of balance

“This hadn't been reported before because no one ever used females, so they weren't in a position to know one way or another,” says Jeffrey Mogil, a pain researcher at McGill University in Montreal, Canada, and co-author of the study.

Mogil says that researchers often exclude female animals from their experiments, assuming that the menstrual cycle makes data from them vary.

Importantly, his team's results may explain why some microglia-targeting pain drugs have failed in human clinical trials. "Maybe they failed because the biology is only true for half the population."

John Wood, a pain researcher at University College London, says that the findings "are of immense importance for understanding and treating pain". It is not yet clear whether the results translate directly to humans, but they raise important questions for the development of pain-killing drugs. "Are there other gender-specific mechanisms in pain pathways, and other distinct gender-specific aspects of central-nervous-system function?"

Mogil and his colleagues are now trying to identify the pain-sensitization pathway in female mice, and hope that their findings will be a wake-up call for others to include more female animals in their experiments.

Last year, the US National Institutes of Health issued guidelines aimed at increasing the percentage of female subjects in pre-clinical trials to redress the balance, yet many labs continue to experiment exclusively on males.

"We're told to use multiple strains and different age ranges, but these things cost money," says Mogil. "Incorporating females into your experimental design costs nothing at all. Hopefully this will help convince people it's worthwhile."

Nature | doi:10.1038/nature.2015.17864

References

1. Sorge, R. E. et al. *Nature Neurosci.* http://dx.doi.org/10.1038/nn.4053 (2015).