PAIN

Too hot to handle? An adult fly model of chronic nociceptionKhuong et al. *Sci. Adv.* **5**, eaaw4099 (2019)

Nociception is the sense that tells animals they are encountering a potentially damaging stimulus. In people, it's called pain. It unfortunately does not always pass quickly. Chronic pain, often accompanied by increased sensitivity to otherwise benign stimuli, is becoming a chronic problem.

Most pain research is conducted with rodents, but nociception is conserved beyond mammals. It can be studied in fruit fly larvae, for example. But larvae exist in a transient state; any 'pain' is therefore transient too. "If we injure these larvae with UV light for example, we can cause a sensitization to noxious stimuli and then study the mechanisms that control this, but it's not long lasting," explained Gregory Neely, a researcher at the University of Sydney, via email. "The larvae turn into adult flies." To see if fly 'pain' can indeed become chronic, the lab needed an adult model.

They initially thought to develop an assay for cold nociception, as people with chronic pain often become sensitive to lower

temperatures. But chill a fly and they just stop moving. Instead, the lab turned up the heat, taking advantage of a hot plate and the fly's natural aversion to surface temperatures above 42 °C. The researchers amputated some legs to then see how peripheral injury might change responses to different temperatures. After recovery, movement was normal relative to that of intact flies, but not thermal sensitivity: for post-injury subjects, a normally tolerable 38 °C became too hot to handle. This response lasted beyond 21 days—a long time for a fly.

As they looked deeper, they expected to see peripheral mechanisms in action, Neely says—"basically, extra 'pain' signals coming from the site of injury." That was not the case. Rather, a neuropathic cascade after the injury was leading to the death of GABAergic neurons in the fly equivalent of a central nervous system. Without these, nociception can go unchecked via a complex mechanism called central disinhibition. A genetic screen revealed that a conserved transcription

factor called *twist*, involved in mesoderm development as well as cancer in mammals, has a role in throwing the death switch.

Neely thinks this could be an evolutionary advantage. "Once an insect experienced a significant injury, then it is permanently sensitized to further danger," he says. Good for a hurt fly, perhaps less so for a modern human. From here, the lab is looking at other ways nerve injuries can affect the flies, as well as how chronic responses might be inhibited in the first place.

The work has also moved to mammals. The lab has been transplanting stem-cell derived GABAergic neurons into the spinal cords of injured mice with pain-relieving results. "Based on these data, we obtained funding to develop this for human use," says Neely.

Ellen P. Neff

Published online: 12 August 2019
<https://doi.org/10.1038/s41684-019-0382-y>

Virus-Antibody-Free Guinea Pigs

"Serving the research community for over 50 years.

Guinea Pig Production is Our Business...

Our Only Business"

- **Excellent quality**
- **Outstanding service**
- **Genuine concern for each customer's particular needs**

Elm Hill Labs
 7 Kidder Road
 Chelmsford, MA 01824

Phone. (800) 941-4349
 Fax. (978) 256-2545
 Email. ehlabs@comcast.net
 Web. www.elmhilllabs.com