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Pain Sensitization Helps Injured Squid Survive Predators

Results suggest an ancient purpose for neural plasticity, new perspective on chronic pain

by Summer Allen on 19 May 2014

It is difficult to imagine anything good about chronic pain. But a clever study shows for the first time that there may be an evolutionary advantage to nociceptive sensitization, the neuroplastic process that may give rise to some chronic pain conditions. In the study, Robyn Crook and Edgar Walters of the University of Texas, Houston, US, showed that nociceptive sensitization in injured squid improved the chances that the animals would survive a swim with a predator. The work was published online in Current Biology on May 8.

"Crook et al. make a compelling case for the adaptive value of nociceptive sensitization, a finding that has profound implications for thinking about the massive problem that is chronic pain in modern societies," wrote Theodore Price and Gregory Dussor of the University of Texas at Dallas, US, in a commentary about the paper, published in the May 19 print issue of the journal.

Crook and Walters knew from their previous work that a minor cut on one arm of the common squid *Loligo pealeii* leads to both visual and tactile hypersensitivity; they also knew that this hypersensitivity was the result of nociceptor sensitization (Crook et al., 2011; Crook et al., 2013). In the current study, the pair, along with colleagues Katharine Dickson and Roger Hanlon, asked whether the sensitization provided a survival advantage. To test this possibility, they injured squid, with or without anesthesia. They also gave anesthesia to a group of uninjured squid as a control.

"In order to separate out the effect of injury being costly and, hypothetically, sensitization being beneficial, we needed a way to interrupt the natural development of sensitization after injury," said Crook. "We had shown previously in *Aplysia*, and also in squid, that if you inject local anesthetic right at the time of doing the injury, you don't get any neural activity right at the injury site at that time, and that stops sensitization from happening."

Six hours later, when the animals were no longer under the effects of anesthesia, the researchers placed the squid in a tank filled with black sea bass, a natural predator. The majority (75 to 80 percent) of uninjured squid survived a 30-minute swim with the bass. Even though the injured squid appeared to behave identically to the uninjured animals, they were preyed on at a significantly higher rate. Injury was

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costly for both groups of injured squid, but the squid that had received anesthesia fared worst: Only 19 percent of those squid survived, compared to 45 percent of the un-anesthetized, injured squid. The anesthetized animals "did much worse than the animals that were injured without anesthesia and who developed sensitization naturally," said Crook. "That shows us that sensitization has a big adaptive benefit for animals in these natural contexts."

"I thought it was really fascinating. It was actually very surprising that the wounded squid with the sensitized nociception actually had an advantage," said Dan Tracey of Duke University, Durham, US, who was not involved in the study. "I was wondering about non-specific effects of the anesthesia, but I think they had nicely controlled for that with the uninjured animals."

"It may be the case that a propensity to develop chronic pain is an evolutionarily encoded feature of complex neural systems," wrote Price and Dussor. They note recent studies indicating that pain plasticity may persist long after injuries have healed, suggesting, "It is the (in)ability to mask this persistent nociceptive plasticity that may be the determining factor in whether or not an injury will lead to chronic pain." (For example, see PRF related news story on Corder et al., 2013, and PRF related news story on De Felice et al., 2011.)

Indeed, treatments for chronic pain that do not take these primitive sensitization mechanisms into account may be set up for failure. As Price and Dussor wrote, "Chronic pain may be a fight against the most ancient forces of evolution, which is bad news for analgesic mechanisms that fail to reverse injury-induced plasticity."

Crook and Walters said that the squid arm injury, which involves cutting the brachial nerve cord and loss of one or more ganglia near the tip of the arm, is a model that may be useful for identifying conserved mechanisms for persistent sensitization following nerve injury. "I think it's very likely that the same mechanisms in squid—which may lack any capacity for true suffering and the emotional component of pain—probably evolved very early and are likely to be used in humans for driving persistent pain," said Walters. "Sensitizing mechanisms in the periphery that are activated after injury may be especially primitive, highly conserved, and important for the survival of squid and humans."

In their commentary, Price and Dussor suggest that studying conserved mechanisms for nociception might be the best way to find new treatments for chronic pain. As evidence, they mention that the mechanistic target of the rapamycin (mTOR) pathway emerged as a target following previous work by the Walters lab in *Aplysia* (Weragoda et al., 2004).

Summer Allen, PhD, is a neuroscientist and freelance writer in Rhode Island, US.

Image: NOAA

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Editors' Pick

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