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Evolution: The Advantage of 'Maladaptive' Pain Plasticity

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Abstract

Following injury, nociceptive systems become sensitized, leading to heightened pain perception. The evolutionary reason for this phenomenon has been hard to pinpoint. A study in squid now suggests that nociceptive sensitization enhances survival from predators.

Anyone who has ever had a sunburn, a sprained ankle or a broken finger understands the ramifications of pain plasticity. Our skin does not normally hurt from a gentle touch but the slightest stroke of sunburned skin can precipitate minutes of agony. Likewise, weight placed on a sprained ankle or typing with a broken finger can change our behavioral patterns for days or weeks. Plasticity in the pain system can be a source of discomfort and, in some cases, prolonged agony. Why would a neurobiological system be capable of causing such a nuisance? The evolutionary advantages of neural systems able to detect damaging or potentially damaging stimuli are obvious; they allow organisms to protect themselves from injury. At the foundation of these systems are specialized sensory neurons, called nociceptors, which detect harmful stimuli, such as noxious heat, cold and pressure. They transduce these signals into messages that can be organized into a behavioral response in the central nervous system. Genetic studies in humans have elucidated factors that are required for the development of nociceptors [1] or channels where loss of function mutations lead to an absence of nociception while a gain of function causes persistent pain in the absence of injury [2]. The absence of nociceptors or a lack of function in these specialized neurons frequently leads to injury-induced loss of extremities, driving home the importance of a functional acute pain system. Following injury the nociceptive system that serves to protect from injury becomes sensitized, leading to enhanced behavioral and physiological responses to noxious (hyperalgesia) and normally innocuous (allodynia) stimuli [3]. This plasticity in the nociceptive system is a crucial factor in chronic pain disorders. It is frequently assumed that this sort of pain plasticity serves a vital survival function for organisms, as it instructs them to avoid further injury during tissue healing. However, this assumption has heretofore been made with little, if any, direct experimental evidence. In this issue of *Current Biology*, Crook *et al*. [4] 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.

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Leading up to the present work, Crook *et al*. [5] demonstrated that squid are endowed with nociceptors that become sensitized in response to injury. Critically, isotonic magnesium chloride ($MgCl_2$), an anesthetic in squid, completely blocks nociceptor activity induced by injury and, more importantly, long-term sensitization induced by experimental crush injury to the squid fin [5]. Sensitization of nociceptors was observed in squid with natural injuries acquired during interactions with other squid and these injuries even led to spontaneous activity in these normally quiescent sensory afferents. As in humans and common laboratory species, such as rodents, plasticity in squid nociceptors manifests behaviorally as mechanical hypersensitivity [5], suggesting a remarkable conservation of hyperalgesic responses across the animal kingdom.

In a brilliant turn on their groundbreaking work, Crook, Walters and colleagues [4] used these findings to design experiments that test the hypothesis that nociceptive plasticity provides a survival advantage for injured squid. The key to the experimental design is the use of $MgCl_2$ at the time of injury. This leaves the squid with an injured arm but a lack of nociceptive plasticity, therefore allowing the effect of nociceptive plasticity to be experimentally isolated [4,5]. The investigators exposed squid with injury and nociceptive plasticity, squid with injury but no nociceptive plasticity — because it was blocked with $MgCl_2$ exposure at the time of arm injury — and uninjured squid to a natural predator, black sea bass. Although the experimenters were unable to detect differences in the gross behavioral patterns of injured versus uninjured squid, black sea bass oriented to injured squid preferentially. Injured squid with nociceptive sensitization became alerted to predatory black sea bass more quickly than uninjured squid and began evasive maneuvers earlier than uninjured squid. Remarkably, injured squid without nociceptive sensitization failed to become alert to predator orientation as rapidly and these squid also did not begin evasive maneuvers as quickly as injured squid with nociceptive sensitization. The consequences of this behavioral deficit in squid where nociceptive plasticity was blocked were dire. These squid escaped attack less frequently and their survival rate was lower than for injured squid with intact nociceptive sensitization. Hence, plasticity in the nociceptive system of squid endows these animals with a distinct survival advantage after injury, providing the first experimental evidence for the adaptive value of pain plasticity and hyperalgesia.

These findings have profound implications for pain neuroscientists and clinicians and, we will argue, for neurobiology in general. It is hard to attend a pain conference or to read a pain textbook without encountering a statement to the effect that pain plasticity and its manifestations, hyperalgesia and allodynia, occur in order to teach the organism to protect itself during the healing process. To our knowledge, this has always been an assumption made without direct experimental evidence. Scientists, clinicians and textbook authors now have a citation to place behind this statement.

Chronic pain affects hundreds of millions of people in the developed world. In the United States the cost of healthcare and lost productivity for chronic pain is higher than for cancer, diabetes and heart disease combined [6]. These are staggering statistics for a mounting health crisis. The work of Crook *et al*. [4] places the problem of chronic pain in a new context. Clearly there is a survival advantage to pain plasticity and this pain plasticity can arise from even minor injuries — recall that injured squid in this study had no obvious

behavioral deficit, unlike a human with a damaged lumbar disc. If this plasticity indeed serves as a vital survival adaptation, does this plasticity resolve when the injury has healed? While it may seem that this should be the case, recent evidence from rodent models of chronic pain suggest that pain plasticity, especially in nociceptor physiology, may persist long after an injury has healed [7–9]. This does not mean that every injury will cause chronic pain. Rather, it now appears to be the case that endogenous analgesic mechanisms have developed to mask the presence of persistent nociceptive plasticity [7,8]. This includes adaptations in spinal cord opioid systems [7] and mechanisms arising from brain stem centers involved in descending pain modulation [8]. These preclinical findings are paralleled by clinical work suggesting deficits in pain modulation circuits as a causative factor in some chronic pain conditions [10]. Hence, it may be the case that a propensity to develop chronic pain is an evolutionarily encoded feature of complex neural systems. 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.

While therapeutic development efforts are underway to target transducers, opioid systems and descending pain modulation, the work of Crook *et al*. [4] suggests a different way: targeting the evolutionarily defined mechanism underlying nociceptive plasticity for the reversal of chronic pain states. Here, the long-standing work of the Walters lab provides crucial insight. From sea slugs, *Aplysia californica*, to squid, *Doryteuthis pealei* (Figure 1), this laboratory has provided evidence for mechanisms involved in sensitization of nociceptors in a diverse range of neurobiological model organisms [11,12]. One highly conserved mechanism — translation control via the mechanistic target of rapamycin (mTOR) pathway — has emerged from this work [13]. We now know that mTOR [14–16], and other translation regulation mechanisms [17], play a key role in the initiation and maintenance of nociceptive plasticity and modulation of these pathways is capable of reversing pain plasticity in mammalian pain models. Although the clinical implications of these findings are unknown, this presents a powerful new paradigm for discovery in the pain arena.

One last implication of the work of Crook, Walters and colleagues [4,5] involves the place of nociceptive sensitization in the evolution of neuronal plasticity. It has not gone unrecognized that molecular mechanisms of pain plasticity are shared with learning and memory [18]. Translation control is a striking example [19], as is the prominent stature of long-term potentiation as a mechanism of memory and central sensitization in pain pathways [20]. Is it possible that these molecular plasticity mechanisms first evolved along nociceptive pathways as an adaptation to enhance survival of injured organisms? Since it is the case that such nociceptive systems are required to sense potential damage in the first place, and the transducers of these pathways are evolutionarily ancient, this possibility cannot be discounted. 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.

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Figure 1.

A model for pain plasticity.

The squid Doryteuthis pealei used in the study by Crook *et al*. [4]. (Image: Roger Hanlon, MBL.)