mammalian brain, suggesting that the pallium of birds is functionally equivalent to part of the mammalian cerebral cortex.

In the new study, length neurons were also located in the same region of the crow's brain as the number neurons, similarly to the monkey study. Moreover, it turns out that these neurons can be tuned to respond to experimentally defined length categories 'long' and 'short' in experiment 1, and 'short', 'medium', and 'long' in experiment 2. The neuron recording methodology does not reveal whether exactly the same neurons have been re-tuned, but evidence from an earlier study of *numerical* categories suggests that number neurons can be tuned by experience[7].

This study raises interesting and important questions. Are length neurons present at birth or do some general purpose neurons, perhaps general purpose 'quantity' neurons, get shaped by experience into length-specific neurons that can selectively respond to environmentally relevant length categories? There is indirect evidence for the former hypothesis from the discovery of number neurons in the pallia of other creatures without a neocortex — newly-hatched chicks[8] and larval zebrafish[9]. We don't yet know whether length neurons, or other pallial neurons that are tuned to continuous environmental quantities, such as time or area, are present in chicks or zebrafish, or indeed whether such neurons can be re-tuned to new environmentally relevant categories, but the pioneering study by Wagener and Nieder shows how we could find out.

DECLARATION OF INTERESTS

The author declares no competing interests.

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Pain: The agony and the AstC

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Pain serves critical biological functions, but under some circumstances it is best suppressed. A new study identifies a channel, a neuropeptide, and a pair of neurons in the fly brain that suppress pain.

'Pain' comes from Poena (Ποινή), who was a Greek goddess, or personified spirit, of punishment. Her fury is vast in scale: some 20% of Americans suffer chronic pain[1]. Current therapies are limited in efficacy and carry risks such as addiction. Clearly there is a critical need for research into mechanisms underlying pain and means of suppressing it. A new study by Liu *et al.*[2] in this issue of *Current Biology* identifies a pair of neurons in the fly brain that attenuate pain: they are aptly named 'Epi neurons' after the Greek goddess Epione (Ἠπιόνη), the goddess of soothing.

The study began with the development of an ingenious behavioral assay. In this respect, Liu *et al.* follow a tradition established half a century ago by Seymour Benzer, the legendary founder of the field of *Drosophila* neurogenetics[3,4]. Flies are placed on a hot plate, and the percentage of flies that jump within ten seconds is measured — a convenient measure of thermal pain. The percentage of jumping flies increases with increasing temperature, and nearly all flies jump at 45°C or so.

Liu *et al.* then screened a collection of fly lines, in each of which a subset of neurons was chronically activated by expression of a bacterial sodium channel. Activation of most neurons had no effect, but activation of neurons expressing the *Allatostatin C (AstC)* gene decreased the percentage of jumping flies. This finding suggested that in wild-type flies, neurons that express *AstC* reduce the response to heat; when activated artificially, these

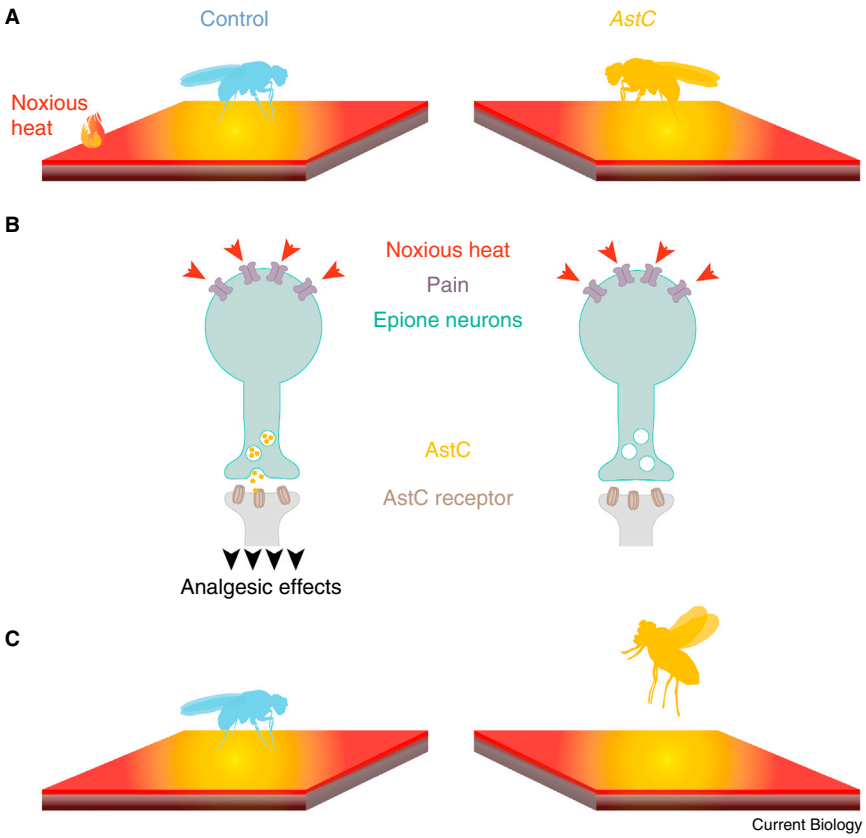

Figure 1. Suppression of pain by Epione neurons via the Pain channel and the AstC neuropeptide.
(A) A fly, either a control or an AstC mutant, is placed on a hot plate. (B) Noxious heat is detected by Pain channels, which are a kind of TRP channel, in Epione neurons. The precise location of Pain channels in Epione neurons awaits definition. In the control fly, AstC neuropeptides are secreted and mediate analgesic effects. The identities of the downstream neurons remains unknown. AstC is not produced in the mutant. (C) The control fly, soothed by the activity of the Epione neuron, does not jump from the noxious heat. The mutant fly, lacking the soothing effects of the Epione neuron, leaps into the air.

AstC neurons reduce the pain response further, such that fewer flies jump off the hot plate. Hence the name Epi neurons, for their ability to soothe pain.

Remarkably, there are only two Epi neurons in the entire fly brain, a bilaterally symmetric pair with large cell bodies. Dendrites of these neurons are distributed widely across the fly brain, including regions dedicated to the fly's senses of sight and smell. Axons are also widespread and similarly extend to regions dedicated to vision and olfaction. However, many axons are sent to the ventral nerve cord, the fly's equivalent of a spinal cord[5]. Here, in the ventral nerve cord, Epi axons likely function in the descending control of motor output.

How do these two neurons suppress the response to heat? First, Epi neurons express a transient receptor potential (TRP) channel called Painless (Pain). David Julius and colleagues showed in classic work years ago that a TRP channel detects noxious heat in mammals[6]. Daniel Tracey, Seymour Benzer, and colleagues showed that Pain detects noxious heat in *Drosophila*[7]. Interestingly, Liu *et al.* found that Pain acts in the response of Epi neurons. Flies that lack the *pain* gene jumped more frequently in response to high temperatures than control flies. Moreover, Pain is required in Epi neurons for pain suppression, as shown by RNAi lines that knock down *pain* specifically in Epi neurons. Thus, rather than mediating escape from pain, in Epi neurons this TRP channel appears to mediate the suppression of pain.

Expression of the Pain channel in Epi neurons can explain how they detect heat, but how do Epi neurons suppress thermal pain? Epi neurons produce AstC, a neuropeptide. Liu *et al.* created an *AstC* mutant and found that its jump response increased (Figure 1), indicating that AstC is required for pain suppression. Moreover, *AstC* is required in Epi neurons for pain suppression, as shown by RNAi-mediated knockdown of *AstC* specifically in Epi neurons. Reciprocally, when *AstC* expression was increased in Epi neurons, the percentage of jumping flies decreased. Thus, the function of Epi neurons in suppressing the response to heat depends on *AstC*.

These and other experiments suggested a model in which Epi neurons detect heat via Pain, and then release AstC on other neurons to mediate pain suppression. In support of this model, live imaging of Epi neuron activity shows that these neurons are activated at high temperatures. This activation is eliminated in the *pain* mutant. Also consistent with the model, experiments with an anti-AstC antibody provided strong evidence that Epi neurons exposed to heat release AstC.

Why does the fly have a mechanism to suppress thermal pain? Liu *et al.* suggest that it may allow flies to enter warm environments in which they can feed or avoid predators. In this regard, it would be interesting to examine Epi neurons in *Drosophila* species such as *D. mojavensis* that have adapted to the desert. It will also be interesting to see whether Epi neurons and their molecular constituents evolve in response to climate change.

It is striking that there are but two Epi neurons in a brain of ~200,000 neurons[8]. There are hundreds of each kind of photoreceptor cell, and tens of most kinds of olfactory receptor neuron. Evidently two heat-detecting cells can drive the pain suppression response delineated by Liu *et al.* This finding raises interesting questions, both theoretical and empirical, about redundancy of neurons in the nervous system.

The complex anatomy of the Epi neurons also invites questions. What information are they collecting from the visual and olfactory systems? What information are they sending to these systems? Is pain suppression modulated by other sensory signals, or perhaps by the internal state of the animal? Could Epi neurons have additional functions beyond pain suppression?

Should those who wish to help the countless humans suffering from chronic pain be interested in fruit flies that don't jump off hotplates? Yes. Not only are TRP receptors common to flies and humans, but AstC is related to the human neuropeptide somatostatin, which is implicated in the inhibition of pain[9–14]. Moreover, AstC receptors in the fly are related to human opioid receptors, which act in pain suppression[13–17]. These commonalities raise the intriguing possibility that further work in the fly could provide new targets useful in treating pain in humans, and ultimately new additions to the pharmacopeia of pain medications.

In a larger sense, Liu *et al.* have provided an excellent example of how fly neurogenetics can provide an intriguing new perspective on a topic that underlies a massive human health problem. Conversely, they have provided further evidence to support the conviction of Seymour Benzer that humans are an excellent model for understanding the fly.

In summary, Liu *et al.* have identified a remarkable pair of neurons in the fly brain. The study has elegantly revealed that these neurons have co-opted a TRP channel to suppress pain rather than enhance it. The work has further shown that these neurons use the neuropeptide AstC to mediate suppression. Taken together, the study has consequences for the battle of the goddesses and could even help the Goddess Epione to prevail.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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