mice, but not in PACAP-deficient mice (Markovics et al., 2012). These results suggest that PACAP is an important mediator of light aversion and meningeal blood flow regulation.

A link has also been reported between migraine phase and changes in plasma PACAP38 levels (Tuka et al., 2013). Plasma PACAP38 immunoreactivity was lower in interictal migraine patients than in a healthy control group. By contrast, PACAP38 and CGRP concentrations were elevated in the iccal phase relative to the attack-free period in 21 migraineurs. A negative correlation was observed between interictal PACAP38 level and overall disease duration. Plasma PACAP38 release in the ictal phase was significant only in menstruation cycle-independent migraineurs and those patients with no other chronic pain condition, such as lower back pain, lumbar or arthrosis. This study thus revealed a clear association between migraine phase and changes in plasma PACAP38 levels.

The results obtained by Amin et al. (2014) will have considerable scientific impact, elegantly demonstrating, in a head-to-head study, the differences between PACAP-38 and VIP-related migraine attacks, including differential effects on extracranial vasodilation. Their observations are key milestones for elucidating the role of PACAP and the mechanism of migraine, and will pave the way for further research into therapies tailored to specific causes of the disease.

László Vecsei,1,2 Bernadett Tuka1,2 and János Tajti1
1Department of Neurology, University of Szeged, Szeged, Hungary
2MTA-SZTE Neuroscience Research Group, Szeged, Hungary

Correspondence to: László Vecsei
E-mail: vecsei.laszlo@med.u-szeged.hu

doi:10.1093/brain/awu014

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Deepening understanding of the neural substrates of chronic pain

Chronic pain has been labelled the silent health crisis, afflicting hundreds of millions of people worldwide. Chronic pain causes more disability than cancer and heart disease, and the annual monetary cost of treatment and lost productivity is above $500 billion per annum in the United States alone (Institute of Medicine, 2011). Once considered simply a response to disease or injury, chronic pain is increasingly recognized as a group of mechanistically separable nervous system processes produced and maintained by a variety of abnormal cellular signalling pathways (Woolf and Salter, 2000).

A growing number of signalling pathways in the peripheral and central nervous systems have been implicated in chronic pain, along with neuron–glia as well as neuron–neuron interactions (Beggs et al., 2012b), and genetic sensitivity (Mogil, 2012) coupled with epigenetic modulation (Stone and Szýf, 2013). Nevertheless, a core unresolved question is which neurons in the pain processing and transmission circuitry in the spinal cord provide the pathological output believed by most to drive the brain’s pain network in chronic pain. And how is the firing activity of those spinal cord neurons altered? In the current issue of Brain, Yves De Koninck and colleagues take a major step forward in answering these questions through their elegant investigation of de novo changes in neurons in the spinal dorsal horn after peripheral nerve injury (Lavertu et al., 2014). The authors leveraged work from a number of groups that had indicated that loss of CI−-mediated inhibition, particularly in neurons in the superficial laminae of the dorsal horn of the spinal cord (Moore et al., 2002; Coull et al., 2003), is critical for chronic pain hypersensitivity. In particular, De Koninck’s group had previously discovered that disinhibition may come about through downregulation of the function and/or expression of KCC2, the K-Cl co-transporter.
responsible for maintaining intracellular Cl\(^-\) at the low concentration needed for effective inhibition by Cl\(^-\)-permeable inhibitory channels gated by GABA or glycine (Coull et al., 2003). Their previous work had implicated disinhibition of one subpopulation of output neurons: those in lamina I of the dorsal horn that project to the lateral parabrachial nucleus (Keller et al., 2007), a subpopulation considered crucial in chronic pain. In this most recent work, the De Koninck group examined neurons that comprise the other major neuronal projection pathway to the brain, the spinothalamic tract, and report some provocative findings.

In recordings from neurons in the deep dorsal horn that were definitively identified as projecting to the thalamus, Lavertu et al. (2014) performed highly detailed, quantitative evaluation of the relationship between mechanical pressure to the skin (the ‘input’) and spike discharge (the ‘output’) for each cell. This ‘neurometric’ approach relied on a force-feedback mechanical transducer based on a design pioneered by John Chubbuck in the mid-1960s. The quantitative input-output data for the neurons were subjected to multivariate analysis which, in naïve animals, yielded two distinct clusters. One cluster has a relatively low mechanical threshold and is broadly tuned, corresponding to the so-called wide-dynamic range (WDR) neurons in previous qualitative or semi-quantitative studies. The other cluster has a much higher mechanical threshold and is steeply tuned, corresponding to nociceptive-specific (NS) neurons. Applying the neurometric approach to spinothalamic tract (STT) neurons after peripheral nerve injury, Lavertu et al. (2014) discovered that there were three rather than two clusters. Two of these corresponded to the WDR-STT and NS-STT clusters in naïve animals, but the third cluster (called NEW-STT) showed emergent properties deduced to result from a lowering of the mechanical threshold with a parallel shift in input-output of nociceptive-specific neurons. Strikingly, about two-thirds of the NS-STT neurons, well-known to occur after nerve injury, might not be necessary for neuropathic pain. Finally, manipulations to restore inhibition after peripheral nerve injury can reverse behavioural pain hypersensitivity (Coull et al., 2003, 2005; Asiedu et al., 2010; Lavertu et al., 2014). Therefore, the normal capacity of the dorsal horn sensory network to mask the excitatory cross-talk appears to be intact for long time periods after the injury, underneath an ongoing drive to unmask the cross-talk. Thus, reconstituting the inhibitory masking may be an approach to treat chronic neuropathic pain.

For neurons in spinal lamina I, the peripheral nerve injury-induced ongoing drive to unmask innocuous-to-nociceptive cross-talk occurs via a core neuron-microglia-neuron signalling cascade (Tsuda et al., 2003; Beggs et al., 2012b). Central to this cascade is de novo expression of the purinoceptor P2X4 by microglia, which, when activated by ATP, causes these cells to increase both the synthesis and release of brain-derived neurotrophic factor (BDNF) (Trang et al., 2009). Release of BDNF is hypothesized to stimulate its cognate receptor, TrkB, on lamina I neurons leading to the suppression of KCC2 and consequent disinhibition (Coull et al., 2005). The findings of Lavertu et al. (2014) open up the possibility that microglia-derived BDNF may also mediate the conversion of deep NS-STT to NEW-STT neurons after peripheral nerve injury. This scenario would be consistent with findings that eliminating microglia-derived BDNF prevents mechanical pain hypersensitivity induced by peripheral nerve injury (Beggs et al., 2012a). Reversing Cl\(^-\)-mediated disinhibition reverses, and eliminating microglia-derived BDNF prevents, the paradoxical hyperalgesia caused by administering morphine and other opiates (Ferrini et al., 2013). Thus, it is possible that conversion of NS-STT neurons to NEW-STT neurons might contribute to opioid-induced hyperalgesia, as well as to neuropathic pain hypersensitivity.

With two types of nociceptive projection neuron now showing stereotypic alteration of responses after peripheral nerve injury, the question arises whether nociceptive lamina I neurons projecting to the lateral parabrachial neurons, or nociceptive neurons in the deep lamina V projecting to the thalamus, or both, are necessary for neuropathic pain hypersensitivity. The lowering of the mechanical threshold to innocuous stimulation, the accentuation of responses to noxious stimulation and the induction of spontaneous activity in both populations appears sufficient for
either to serve as a neural substrate for the three cardinal signs of neuropathic pain hypersensitivity—alldynia, hyperalgesia, and spontaneous pain. Only selective inactivation of one class of neuron, but not the other, will address the question of necessity. At present, answering this question is not possible, but there is light at the end of the tunnel, literally. With advances in optogenetic methods to inactivate, as well as to activate, specific subsets of neurons defined molecularly or by site of projection, or both, one can readily envisage that there will be an answer to this deep question about pain mechanisms in the not too distant future.

Funding

Work of the author is supported by the Canadian Institutes of Health Research. The author holds a Canada Research Chair (Tier I) & is the Anne & Max Tanenbaum Chair in Molecular Medicine at the Hospital for Sick Children.

Michael W. Salter
Hospital for Sick Children,
Toronto, Ontario, Canada

Correspondence to: Michael W. Salter
E-mail: michael.salter@sickkids.ca

doi:10.1093/brain/awu028

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