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Editorial

Laser guns and hot plates☆

Noxious heat stimuli are frequently used to study the nociceptive system, because they activate a nociceptive-specific transduction mechanism (Julius and Basbaum, 2001). Nociceptive nerve endings can be heated by either thermal conduction or thermal radiation. Both methods have their advantages and disadvantages. Conductive heating allows control over the temperature at the stimulator–tissue interface, but concomitant stimulation of low-threshold mechanoreceptors is a potentially confounding factor and uniform contact between the stimulator and the uneven surface of the skin depends critically on thermode pressure. Radiant heating avoids these problems, but variations in baseline temperature can lead to misinterpretations (Tjolsen et al., 1988).

Cerebral potentials evoked by noxious heat stimuli allow to study human nociceptive brain processing with outstanding temporal resolution, and information from their source analysis is complementary to fMRI and PET results (Peyron et al., 2002). Although few early studies used thermodes, the breakthrough in this field came with the introduction of infrared laser stimulators (Bromm and Treede, 1984; Carmon et al., 1978), and laser-evoked potentials now have attained an important position in both basic and clinical research (Cruccu et al., 2004; Treede et al., 2003).

In a previous issue of PAIN (volume 115, issue 3), Granovsky et al. (2005) report brain potentials evoked by a thermofoil thermode that allows much faster heating rates (nominally up to 70 °/s) than conventional Peltier thermodes. Similar rapid thermodes had been first developed in Aalborg (Chen et al., 2001). Granovsky and coworkers exploited the different threshold temperatures of C-fiber nociceptors (41 °C) and A-fiber nociceptors (46 °C) to study the difference in nociceptive innervation between hairy and glabrous skin. They report that late potentials consistent with A-fiber conduction velocities were evoked by 51 ° stimulation and ultralate potentials consistent with C-fiber conduction velocities were elicited by 41 °C stimulation in hairy skin. For glabrous skin, they found only ultralate potentials for both stimulus temperatures, consistent with the reported absence of A-fiber nociceptors with a rapid heat response (type-2 AMHs) from glabrous skin (Treede et al., 1995).

Granovsky and coworkers used an elegant approach to estimate conduction velocities for evoked potentials. They intentionally recruited subjects with different arm lengths and used the slope of the regression of evoked potential latency to arm length for their conduction velocity estimate. In addition, they used the conventional technique of stimulating two sites (hand and forearm). Whereas conduction velocities for hairy skin had been determined previously by several authors, the reported values for glabrous skin are new. To overcome the lack of glabrous skin at proximal sites, the authors made the assumption that ultralate potentials in hairy and glabrous skin are mediated with the same conduction velocity and estimated it from distal glabrous to proximal hairy skin, yielding 1.7 m/s.

Some caveats apply to their conduction velocity estimate for heat nociceptors in glabrous skin: (1) The method is indirect and provides an estimate, not a measurement of conduction velocity. (2) There was a large variability depending on the method used, hence more studies are mandatory, before accepting that it is always in the C-fiber range. (3) It is not clear to what extent warm receptors contribute to the C-fiber responses.

When dealing with rapid signals such as evoked potentials, precise control of stimulus timing is essential. Taking the conduction velocity of 1.7 m/s and the conduction distance of 737 mm, the neuronal signal will need at least 434 ms to reach the spinal cord. The authors argue that the peak latency of the ultralate potential of 485 ms leaves 51 ms for signal conduction from the spinal cord to the brain. These considerations must contain some error, because nociceptors are not activated at the beginning, but during the heat ramp (here: 190 ms). Had the trigger been at the onset of the temperature rise, as stated in the paper, the afferent volley would still be travelling in the peripheral nerve at the time of the evoked potential peak. More likely, the trigger coincided with the end of the heat ramp, but then this important timing parameter is specified incorrectly.

☆ Please see related article in the June issue of PAIN; Granovsky et al., PAIN 115/3, pp. 238–247.

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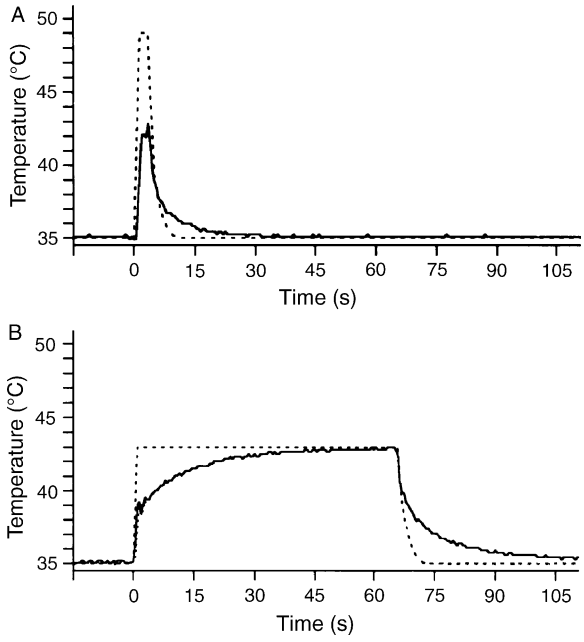

Fig. 1. What you see is what you get? Comparison of nominal temperatures from thermocouples within a contact heat device (dashed lines) with actual skin surface temperature recorded with two low-mass thermocouples between the stimulator and the skin (solid lines). A: Skin temperature was raised by 4 °C/s to a short plateau of 43 °C, if the target temperature was set to 49 °C and the rate of temperature change to a nominal 10 °C/s. B: With a longer stimulus duration, skin surface temperature approached the target temperature (here: 43 °C) after 1 min. The change in slope is due to the feedback circuit, which relies on the internal temperature reading that erroneously signals that the target temperature has been reached after 2 s. (Modified from Magerl and Treede, 1996).

Contact heat stimulators receive a feedback temperature signal from a thermocouple embedded in the surface of the stimulator, hence controlling the temperature at that location. Nociceptive nerve endings, however, terminate between 20 and 570 μm below the skin surface (Tillman et al., 1995). Even at thermal equilibrium, temperature at the nerve terminals is lower than at the stimulator surface, since subcutaneous tissue acts as a heat sink. Under dynamic conditions, skin temperature changes can be substantially slower than temperature changes at the stimulator surface (Fig. 1). This problem becomes worse as the heating rate increases (Magerl and Treede, 1996; Tillman et al., 1995). Thus, the biggest advantage of contact heat stimulators (precise temperature control) is lost at higher temperature rise rates. With the device used by Granovsky and coworkers, neither the rate of temperature change nor the final temperature reached at the skin surface can be estimated from an internal thermocouple. Unfortunately, the authors do not report any intracutaneous or skin surface temperature recording. Before the CHEPs device can be used clinically, validation of the physical properties of the stimuli that it delivers is essential.

The infrared radiation of modern solid-state lasers like thulium-YAG (wavelength 2.01 μm, extinction length 360 μm) or neodymium-YAP (wavelength 1.34 μm, extinction lenght >500 μm) directly reaches the nociceptive nerve terminals, leading to rapid activation of nociceptive afferents with stimulus durations as low as 1 ms (Iannetti et al., 2004; Spiegel et al., 2000). This in turn increases the signal-to-noise ratio, enabling the study of smaller neuronal signals. These lasers are commercially available and licensed in Europe or the USA for use in clinical neurophysiology.

A modern hot plate, such as the one used by Granovsky and coworkers (2005), can heat the skin surface fast enough for evoked potential studies, but the applied temperature waveform is delayed and attenuated by thermal conduction between skin surface and nociceptive nerve terminals. These distortions prevent controlling the temperature at the receptor level. Modern lasers with wavelengths chosen to yield a penetration depth matched to the depth of nociceptive nerve terminals have several advantages that are probably worth the extra effort needed to operate a ‘laser gun’ (eye protection, notification of regulatory authorities). No matter which mode of heating will prevail in clinical practice, heat-evoked potentials will become more important in the near future for documentation of hypoalgesia as an objective sign in neuropathic pain.

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