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Sensitization and habituation of AMH and C-fiber related percepts of repetitive radiant heat stimulation

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Abstract

Objective: Pain perception involves neuronal plasticity at peripheral and central stages, resulting in sensitization or habituation, depending on intensity and temporal features of stimulation. Concurrent assessment of perceptual change over different time spans is therefore important for understanding the dynamics of pain processing.

Methods: A new psychophysical procedure was established to assess sensitization and habituation during repetitive radiant heat stimulation. Short-term perceptual change (<1 min) during trials with 10 stimuli applied at 3 frequencies (0.2–0.6–1.8 Hz) and 3 intensities was assessed for AMH-II or C-fiber related percepts. Perceptual changes were monitored for medium-term (1–15 min) and for long-term (15–90 min) time spans.

Results: Short-term sensitization occurred only at frequencies above 0.3 Hz and was affected by both stimulus frequency and intensity, but the AMH-fiber related sensitization depended on intensity only above 0.6 Hz. Multiple stimulation of the same skin area during medium-term time spans resulted in habituation. No long-term perceptual changes occurred.

Conclusions: The procedure permits concurrent assessment of short-term sensitization and medium-term habituation, assumed to be related to spinal windup and cutaneous nociceptive fiber fatigue, respectively.

Significance: The method is suitable for quantitative sensory testing of dynamic pain processing over different time spans, relevant in clinical testing of pain and in drug assessment.

Keywords: Perceptual sensitization; Habituation; Temporal summation; Radiant heat pain; Quantitative sensory testing; Psychophysics

1. Introduction

Repetitive nociceptive stimulation established for microneurographic studies in animals has been transferred to human pain research (Handwerker and Kobal, 1993), leading to several perceptual changes, and in particular reversible sensitization within seconds, similar to tonic stimulation (Kleinböhl et al., 1999). Experimental pain models applying repetitive or tonic stimuli have been repeatedly used for psychophysical investigation of chronic pain syndromes, like neuropathic (Eide, 2000) or musculoskeletal pain (Graven-Nielsen et al., 2000; Kleinböhl et al., 1999; Maixner et al., 1998; Staud et al., 2001). According to these data, an augmented perceptual sensitization, compared with healthy controls, is a common clinical marker in some chronic pain syndromes (for a review, see Eide, 2000).

The reversible sensitization which is achieved within seconds by temporal summation of single stimuli at repetition rates faster than 0.3 Hz is supposed to be caused by activation-dependent neuronal plasticity in spinal dorsal horn neurons, so-called windup (Mendell, 1966; Woolf and Salter, 2000). C-fiber mediated excitation of these neurons following intensive sustained or repeated stimulation leads to prolongation and accumulation of slow excitatory post-synaptic potentials (EPSPs) within several seconds.

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The depolarization of spinal dorsal horn neurons is additionally intensified by *N*-methyl-D-aspartate (NMDA) sensitive ion channels, leading to an increase in discharge frequency (windup) over time (Mendell, 1966; Woolf and Salter, 2000). This process of short-term neuronal plasticity is reversible; it occurs within less than a minute and can be blocked by administration of NMDA-antagonists in animal experiments (Woolf and Thompson, 1991).

Temporal summation in human perception and windup in spinal dorsal horn neurons share several characteristic features. Evoked by the same experimental models, both phenomena occur reversibly within less than a minute at stimulus rates faster than 0.3–0.5 Hz (Nielsen and Arendt-Nielsen, 1998; Price et al., 1994; 1977) and both can be suppressed by NMDA-antagonists (Arendt-Nielsen et al., 1995; Price et al., 1994). Temporal summation is therefore assumed to be the perceptual correlate of windup in spinal nociceptive transmission neurons (e.g. Price et al., 1994).

The observation of enhanced temporal summation and perceptual sensitization in chronic pain was interpreted as evidence for a prominent role of spinal windup and the related process at the NMDA-receptor ion channel in chronic pain. This assumption is rejected nowadays because windup is a short-lived and reversible physiological response within normal range, which cannot explain plausibly the long-lasting perceptual changes in chronic pain (e.g. Woolf, 1996). Although it is assumed that windup is not central for the development of chronic pain, the clinical observation of enhanced sensitization as a clinical marker in some chronic pain syndromes remains. This could be explained by other pain-relevant processes altered in chronic pain, which may act in parallel with windup on the level of the spinal cord, or in sequence, on a cerebral level:

(a) A long-term-potentiation (LTP) in spinal nociceptive neurons was discussed as a possible consequence of windup, thus linking the short-term process with long-term alterations in pain processing (Li et al., 1999).
(b) An LTP could also act in parallel with windup, slowing the threshold frequency of windup typically observed at 0.3 Hz (Herrero et al., 1992; Sandkühler, 2000), thus changing the psychophysical temporal summation characteristics.
(c) Cerebral nociceptive neurons may as well show activation-dependent plasticity superimposed on spinal sensitization effects, which is supported by studies showing physiological correlates of sensitization in the brain (Chen et al., 2000; Kleinböhl et al., 2002).
(d) Operant learning, which has been considered a relevant mechanism in pain becoming chronic for a long time now, could modify and enhance the perceived sensitization based on spinal windup, thus explaining enhanced short-term sensitization as well as the long-lasting perceptual changes in chronic pain. We recently presented evidence that perceptual sensitization (and habituation) can be modulated by operant conditioning, inducing long-term changes in pain perception by implicit learning (Hölzl et al., 2005). A 'sensory decalibration', as postulated by Lethem et al. (1983) and others was shown in this study with operant reinforcement of perceptual sensitization, thus proving the important role of sensitization and its operant modulation for long-term changes in pain perception.

These assumed links and interactions of the short-lived sensitization processes with long-term alterations in pain processing could explain why measures of perceptual sensitization are important marker characteristics in clinical pain diagnostics. We therefore stress the importance of experimental pain procedures investigating dynamic change in perception. However, mid- and long-term perceptual effects such as hyperalgesia and habituation interact with short-term sensitization, and there is a lack of psychophysical procedures providing a basis for a selective procedural separation of these different dynamic aspects of pain plasticity.

Perceptual sensitization has been shown with temporal summation models for contact and radiant heat (Nielsen and Arendt-Nielsen, 1998; Price et al., 1977), electrical (Arendt-Nielsen et al., 2000) and mechanical stimuli (Magerl et al., 1998). However, there is controversy as to whether temporal summation applies accordingly for the well-localized sharp, pin-prick such as 'first pain' sensation and the poorly localized dull, burning quality of 'second pain' sensation (Nielsen and Arendt-Nielsen, 1998; Price et al., 1977). Temporal summation for both qualities has been demonstrated, but psychophysical differentiation is intricate due to the complex overlapping of first pain by the temporally-blurred second pain sensation (Nielsen and Arendt-Nielsen, 1998).

Temporal summation during repetitive thermal stimulation has also been interpreted as an artifact due to a slowly rising baseline temperature of the skin during a pulse sequence, applying stimuli to the same skin area (Mauderli et al., 2003; Vierck et al., 1997). The problem arises especially with laser stimulation, for baseline temperature can only be regained by hemodynamic thermoregulation and passive surface heat flux in the skin (Brugmans et al., 1991). During repetitive laser irradiation with constant energy, these processes might be too slow to regain pre-stimulus baseline temperature between pulses, especially at high repetition rates (Brugmans et al., 1991). The resulting gradual increase in baseline skin temperature adds to the constant energy of laser stimuli, thus increasing stimulus temperatures and mimicking 'perceptual sensitization' during stimulus repetition.

While short-term perceptual sensitization and long-term hyperalgesia have received considerable attention, few experimental studies have dealt with habituation or adaptation in the time span of minutes (e.g. Ernst et al., 1986; Milne et al., 1991; Valeriani et al., 2003; 2005). With electrical stimulation, habituation was found in the time