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REVIEW

Translating nociceptive processing into human pain models

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Abstract As volunteers can easily communicate quality and intensity of painful stimuli, human pain models appear to be ideally suited to test analgesic compounds, but also to study pain mechanisms. Acute stimulation of nociceptors under physiologic conditions has proven not to be of particular use as an experimental pain model. In contrast, if the experimental models include sensitization of the peripheral or central pain processing they may indeed mimic certain aspects of chronic pain conditions. Peripheral inflammatory conditions can be induced experimentally with sensitization patterns correlating to clinical inflammatory pain. There are also well-characterized models of central sensitization, which mimic aspects of neuropathic pain patients such as touch evoked allodynia and punctate hyperalgesia. The main complaint of chronic pain patients, however, is spontaneous pain, but currently there is no human model available that would mimic chronic inflammatory or neuropathic pain. Thus, although being helpful for proof of concept studies and dose finding, current human pain models cannot replace patient studies for testing efficacy of analgesic compounds.

Keywords Human pain models · Peripheral sensitization · Central sensitization · Hyperalgesia

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Introduction

Basic research has provided detailed molecular mechanisms for nociception including the crucial steps of transduction processes, spike initiation, action potential conduction, processing in the spinal cord, and finally central processing. Clinical research on the other hand tries to link information on the basic mechanisms to the actual pain patients trying to identify crucial steps linking them to the clinical symptoms and provide targets for therapeutic intervention. Human pain models in healthy volunteers have been developed to facilitate this translational process. Initial approaches to simply use acute noxious stimulation trying to assess analgesic properties of candidate drugs basically failed (Chapman et al. 1965). This early failure has been a major setback for the development of human pain models as it questioned the rationale of the general approach and delayed their development for decades. Meanwhile it has become clear that sensitization of nociceptive processing is one major mechanism that leads to chronic pain conditions. Thus, experimental pain models have been successfully developed that mimic sensitization of primary afferent nociceptors (primary hyperalgesia) and sensitization of spinal processing (secondary hyperalgesia) (Petersen and Schmelz 2008).

Pain models of nociceptor activation

These models activate nociceptors to induce pain without creating peripheral or central sensitization. The simplest approach to assess the pain response is psychophysics: stimuli of controlled intensity are applied to the subjects and their subjective ratings of quality and intensity of the induced sensation are used for the analysis. Most widely

used for mechanical stimulation of the skin are calibrated nylon filaments (von Frey hairs) or metal pins with identical tip, but different weight (Rolke et al. 2006). For phasic mechanical pain, stimulators providing velocity-controlled impact stimuli have been developed (Kohlloffel et al. 1991). In deeper tissues, pressure algometers with larger contact surface are applied, whereas for visceral pain balloon with controlled pressure are in use. For temperature stimulation, well-controlled Peltier systems are available, providing both graded heat and cold stimuli, but their application is mainly restricted to the skin. In contrast to these well-controlled physical stimuli, chemical activation of nociceptors is more problematic. Not only concentration of the algogenic substance, but also area, time course and mode of application are crucial parameters for the activation of nociceptors and the ensuing pain sensation. Common application techniques include injection (intradermal, subcutaneous, and intramuscular), infusion, microdialysis, iontophoresis, epicutaneous application, and blister base application. Advantages of the simple injection technique are well-controlled volume and concentration of the applied substance; however, the injection itself causes pain and might induce unwanted local inflammatory responses. Moreover, for many substances rapid onset and transient time course of nociceptor activation complicates the psychophysical assessment. Prolonged application of substances can be provided by epicutaneous application (Petersen and Rowbotham 1999), which can be facilitated by iontophoresis (direct current enhanced transcutaneous transport) (Hamilton et al. 2000). However, topical application is restricted to small molecules able to penetrate the skin (Hosogi et al. 2006); application results in cutaneous concentration gradients, which are hard to predict and thus absolute local concentrations at the nociceptive endings are basically unknown. Microdialysis or dermal infusion techniques can be used to apply algogens for a prolonged period with a better control of local concentration (Blunk et al. 2004; Eisenbarth et al. 2004; Fairweather et al. 2004; Ikoma et al. 2004); however, both techniques involve local trauma by inserting a needle, which might interfere with the psychophysical assessment of pain.

For cornea and nasal mucosa combined mechanical, chemical and temperature stimulators have been designed using flow of different gases and temperature (Chen et al. 1995; Mohammadian et al. 1997). Flow of CO_2 causes pulses of low pH-induced chemical pain, whereas heated or cooled air provides temperature stimuli and high flow pulses produce mechanical stimulation.

Application of specific agonist provides an interesting tool to test "target engagement": injection of the TRPV1 agonist capsaicin has been reduced by a systemic TRPV1 blocker (Chizh et al. 2007). Albeit some specific agonists can be used in human (Eisenbarth et al. 2004) often endogenous non-specific mediators are used such as ATP (Hamilton et al. 2000) or low pH (Hosogi et al. 2006).

Pain models of neuronal sensitization

Pain models can be classified according to their presumed mechanism (inflammatory vs. neuropathic), the involved tissue (skin vs. muscle vs. viscera), and their time course (acute vs. subchronic). However, mechanistically the most important categories are peripheral or central sensitization. Peripheral sensitization implies that endogenous or exogenous mediators lower excitation thresholds and increase suprathreshold firing in the primary afferent nociceptors. In contrast, central sensitization implies that spinal processing of afferent information is sensitized such that normally non-painful input is causing pain (allodynia) or normally slightly painful stimuli are felt more painful (hyperalgesia). Conceptually, the two forms of sensitization are strictly separated; however, most of the actual pain models are characterized by a combination of peripheral and central sensitization. As an example, topical application of capsaicin will lead to primary sensitization to heat, as measured by lowered heat pain detection thresholds within the stimulated skin (primary hyperalgesia). In addition, the nociceptive barrage to the spinal cord will induce central sensitization, evidenced by mechanical allodynia and hyperalgesia in an area surrounding the stimulation site (secondary hyperalgesia).

Acute peripheral sensitization

Peripheral sensitization can be caused by endogenous or exogenous mediators. Among the exogenous mediators, topical capsaicin application is most commonly used. Capsaicin application activates TRPV1 receptors and sensitizes the local nociceptive endings to heat stimuli. Sensitization of TRPV1 has been extensively studied in animals and can be mediated by phosphorylation of the channel, translocation, use dependent pore widening and increased expression. Human studies did not contribute much to uncover these mechanisms mainly because of their inherent limitations.

A similar sensitization pattern as provoked by capsaicin can be induced by mustard oil application, which supposedly also excites TRPA1 receptors. In contrast, topical menthol application acting on TRPM8 receptors has been used to sensitize cold and cold pain sensation (Wasner et al. 2004). The induced thermal sensitization in menthol models is extensive and robust; however, it is not clear which endogenous mechanism of sensitization is being modelled. Thus, use of these models is basically limited to target engagement studies.

Local sensitization can also be induced by endogenous mediators. Tonic pressure of a skin fold provokes a local inflammatory response such that repetition of the pressure causes increased pain (Forster et al. 1992; Kilo et al. 1995) (Fig. 1). It is unclear as to whether the increased pain of pinching is a true mechanical hyperalgesia or a combination of mechanical stimulation and local ischaemia (Schmelz et al. 1997). Anyway, it is a simple and robust model to test analgesic effects of NSAIDs (Forster et al. 1992; Kilo et al. 1995). Interestingly, the time course of pain induced by a pinch stimulus in human skin correlates to activity in mechano-insensitive C-nociceptors rather than classic polymodal nociceptors (Fig. 1).

Subchronic peripheral sensitization

The pinch model is one of a few causing acute mechanical sensitization, whereas primary mechanical hyperalgesia in other models involving endogenous mediators develops gradually over several hours [e.g. UVB-burn (Gustorff et al. 2004; Hoffmann and Schmelz 1999; Koppert et al. 2004) and the freeze lesion (Kilo et al. 1994; Lotsch and Angst 2003)] (see Fig. 2). While irradiation with UVB is pain free, the application of a −20°C stimulus in the freeze model is painful. It is generally held that these inflammatory models cause mainly local sensitization of nociceptive endings (primary hyperalgesia) restricted to the inflamed tissue. However, with more intense stimulation or larger UVB burns, spontaneous activity in nociceptors can arise leading to increased afferent input and central sensitization (see below) (Gustorff et al. 2004). Mechanistically, among the endogenous inflammatory mediators, prostaglandin E2 may be responsible for early heat hyperalgesia (Miller et al. 1994), whereas longer lasting mechanical hyperalgesia nerve growth factor may be involved (Bishop et al. 2007, 2009).

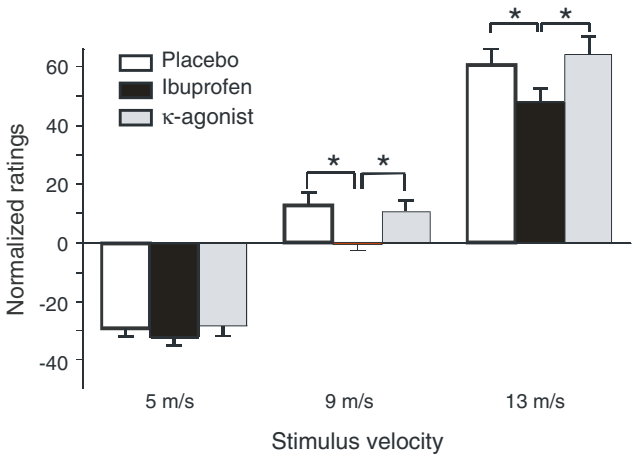

Fig. 2 Reduction of mechanical hyperalgesia following UVB burn by ibuprofen, but not k-opioid agonist. Impact stimuli of 5, 9 and 13 m/s were applied on UVB burns 24 h post-irradiation. Pain ratings were reduced by systemic ibuprofen (600 mg) for the painful stimuli of 9 and 13 m/s velocity. For details, see Bickel et al. (1998)

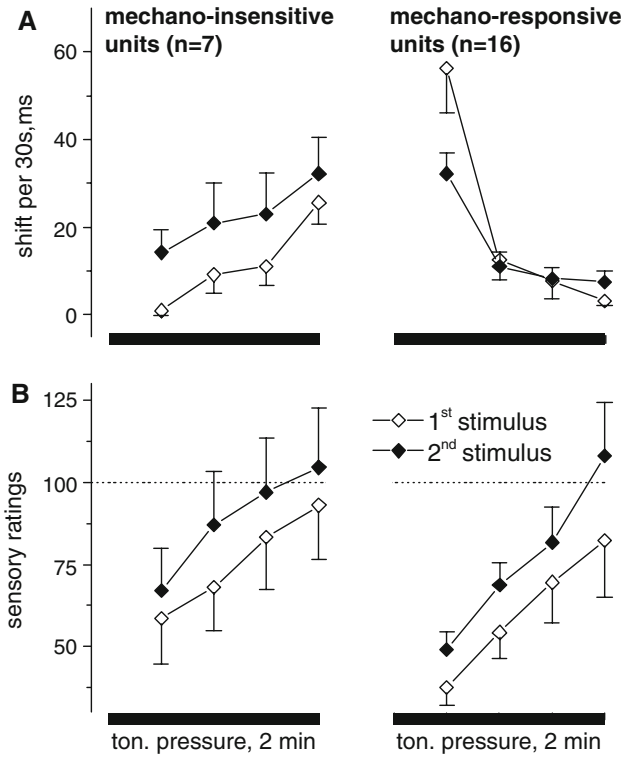

Fig. 1 Activity in different nociceptor classes (**a**) and pain ratings (**b**) and during a 2-min pinch stimulus: activity in single C-nociceptors as assessed by microneurography increased during a 2-min pinching stimulus in mechano-insensitive nociceptors (**a**, *left*), whereas classic polymodal nociceptors showed an adaptation (**a**, *right*). Time course of pain ratings (**b**) correlated to activity in the mechano-insensitive nociceptors, but not to the polymodal nociceptors. For details, see Schmidt et al. (2000)

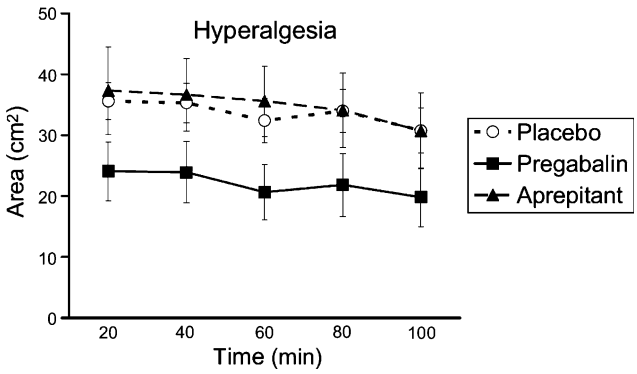

Fig. 3 Pregabalin, but not the NK1 antagonist aprepitant reduces electrically induced area of punctate hyperalgesia nicely correlating to the analgesic effects of pregablin and the lack of analgesic effects of NK1 antagonists in chronic pain patients. For details, see Chizh et al. (2007)

Mechanical hyperalgesia induced by endogenous mechanisms can also be provoked in skeletal muscle by controlled eccentric exercise leading to the delayed onset muscle soreness (DOMS). The exact mechanism leading to hypersensitivity in this microinjury model is unclear und controlled mechanical stimulation of the muscle required more elaborate stimulation techniques. Moreover, pain adapts upon repetitive stimuli in this model which does not mimic most clinical muscle pain states. Anyway, it has been used in pharmacological trials with an analgesic effect being shown for NSAIDs and morphine (Tegeder et al. 2003).

Central sensitization

Central sensitization is a hallmark of neuropathic pain. Several studies have suggested that noxious input from injured nociceptors in the periphery drive the central sensitization process (Devor and Seltzer 1999; Petersen et al. 2000). Indeed, secondary mechanical hyperalgesia to brushing (touch allodynia) or to punctate stimuli (pin prick hyperalgesia) has been shown to vary in spatial extent with the intensity of ongoing pain in neuropathic pain patients (Koltzenburg et al. 1994). In healthy volunteers, activation of nociceptors can induce reversible central sensitization; various stimulation methods have been proposed using electrical (Koppert et al. 2001), chemical (Simone et al. 1989; Simone et al. 1985) or heat stimuli (Cervero et al. 1993; Moiniche et al. 1993; Pedersen and Kehlet 1998; Petersen and Rowbotham 1999). The goal is long-lasting sensitization without tissue-injury. The most commonly used model is injection of capsaicin, which not only can locally sensitize to heating stimuli (peripheral sensitization; see above), but also provokes strong, but transient nociceptor activation, which in turn induces punctate hyperalgesia and touch allodynia as a result of central sensitization. Heating of the skin similarly activates nociceptors and the noxious barrage to the spinal cord leads to central sensitization depending on stimulus intensity and duration (in addition to the peripheral inflammation described above) (Moiniche et al. 1993). Stimulation with 47°C for 5 min (originally 49°C for 5 min) leads to long lasting sensitization, but about 25% of subjects develop blisters. The brief thermal sensitization model (BTS; 45°C for 3 min) provides short lasting sensitization and can be induced 2–3 times at hourly intervals without skin injury. The heat/capsaicin sensitization model combines non-injurious levels of these two stimuli to induce long-lasting central sensitization (Petersen and Rowbotham 1999).

Heating of the skin to 45°C for 5 min activates and sensitizes peripheral nociceptors and is sufficient to induce short lasting central sensitization. This is followed by immediate application of topical capsaicin (0.075%) to further activate and sensitize nociceptors to enhance and prolong the central sensitization. Then mild heating stimuli (40°C for 5 minutes) can be repeated every 40 min to activate the peripherally sensitized nociceptors and provoke a nociceptive barrage to the spinal cord sufficient to maintain the central sensitization for up to 4 h.

Electrical stimuli would appear ideal to provoke nociceptor activation; however, high-current densities are required to excite the high threshold mechano-insensitive C-nociceptors, which are crucially involved in the induction of central sensitization (Schmelz et al. 2000). Using high-current density stimulation pain and central sensitization can be maintained at a stable level for few hours (Angst et al. 2003; Chizh et al. 2007; Koppert et al. 2001; Troster et al. 2006) (Fig. 3). The molecular mechanism for central sensitization using heat, capsaicin or electrical stimulation is not yet clear. However, it appears that a subpopulation of NK1-positive spinothalamic projection neurons is particularly important for the induction of central sensitization (Ikeda et al. 2003; Sandkuhler 2009). On the level of primary afferent, mechano-insensitive nociceptors have been suggested to be crucial for providing the input to cause allodynia and punctate hyperalgesia (Schmelz et al. 2000).

Also, high-frequency stimulation at high-current density for short bursts (five 1-s bursts at 100 Hz at 2 mA, 2 ms) has been used to induce secondary mechanical hyperalgesia (Klein et al. 2004). First, pharmacological tests in this model revealed antihyperalgesic effects of NMDA blockers against electrical stimulation, but not to pin prick hyperalgesia or touch allodynia (Klein et al. 2007).

It should be noted that all the above-mentioned models involve painful stimulation of nociceptive afferent fibres for induction. However, once hyperalgesia is induced, severe ongoing spontaneous pain, which is the main complaint of neuropathic pain patients, is no longer present in most of the models.

Gaps between clinics and models: perspectives

Human pain models have been developed that mimic central sensitization and also peripheral inflammatory sensitization. There is major progress in our understanding of sensitization of transduction proteins occurring especially in inflammatory pain: direct activation and sensitization of sensory proteins by phophorylation can be combined with translocation of transduction proteins and increased expression level.

The link between sensitization in inflammatory models such as UVB burn and clinical inflammatory conditions is considerably good. However, even those models only reflect part of the disease. Still we lack information about the role of trophic factors for the long-term modulation of nociceptor structure and sensitivity. Moreover, the exact

mechanism of impulse generation and determinants of peak frequency and number of action potentials for a given depolarization of the sensory ending are still unknown. There is a complex interaction of voltage-gated sodium and potassium channels with calcium-activated sodium and potassium channels, hyperpolarization induced currents (HCN), sodium potassium pump, and possibly voltage-gated chloride channels. Albeit all these channels and pumps may contribute to spike initiation for the clinical perspectives it needs to be clear as to whether a mechanism is also crucially involved in the generation of pain. Thus, target validation needs to be done in the patients as only the crucial targets can be expected to generate analgesia.

A new development of human pain models with aspects of peripheral and central sensitization without inflammation has emerged recently: intracutaneous injection of nerve growth factor is known to produce mechanical and heat hyperalgesia lasting for several weeks (Dyck et al. 1997); latest results (Rukwied et al. 2008) more clearly characterize the mechanical hyperalgesia as being a combination of lasting static, but not dynamic allodynia (Ochoa and Yarnitsky 1993), cold hyperalgesia and hyperalgesia to mechanical impact and punctate stimuli (Rukwied et al. 2008). The sensitizing effects of NGF include phosphorylation, translocation and upregulation of TRPV1 (Stein et al. 2006; Zhuang et al. 2004) which might be linked to heat hyperalgesia. The molecular mechanisms for mechanical and cold hyperalgesia, however, remain unclear.

Albeit the NGF human pain model appears to generate a combination of symptoms similarly found in pain patients, still it is incomplete as the most relevant symptom of the pain patients, i.e. spontaneous pain, is not mimicked in the NGF model or other human pain models. This essential gap is based on ethical limitations of human models according to which no healthy volunteer can be turned into a chronic pain patient. Irrespective of this limitation, the mechanism leading to spontaneous pain is unknown and even the site of origin is debated. Thus, there would not even be a defined mechanism that could be modelled. In summary, human pain models can mimic certain aspects of chronic pain patients including peripheral and central sensitization, whereas other aspects, such as spontaneous pain and structural changes of the nervous system can only be investigated directly in the pain patients.

References

Angst MS, Koppert W, Pahl I, Clark DJ, Schmelz M (2003) Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. Pain 106:49–57

Bickel A, Dorfs S, Schmelz M, Forster C, Uhl W, Handwerker HO (1998) Effects of antihyperalgesic drugs on experimentally induced hyperalgesia in man. Pain 76:317–325

Bishop T, Hewson DW, Yip PK, Fahey MS, Dawbarn D, Young AR, McMahon SB (2007) Characterisation of ultraviolet-B-induced inflammation as a model of hyperalgesia in the rat. Pain 131:70–82

Bishop T, Ballard A, Holmes H, Young AR, McMahon SB (2009) Ultraviolet-B induced inflammation of human skin: characterisation and comparison with traditional models of hyperlagesia. Eur J Pain 13:524–532

Blunk JA, Schmelz M, Zeck S, Skov P, Likar R, Koppert W (2004) Opioid-induced mast cell activation and vascular responses is not mediated by micro -opioid receptors: an in vivo microdialysis study in human skin. Anesth Analg 98:364–370

Cervero F, Gilbert R, Hammond RGE, Tanner J (1993) Development of secondary hyperalgesia following nonpainful thermal stimulation of the skin a psychophysical study in man. Pain 54:181–189

Chapman LF, Dingman HF, Ginzberg SP (1965) Failure of systemic analgesic agents to alter the absolute sensory threshold for the simple detection of pain. Brain 88:1011–1022

Chen XJ, Gallar J, Pozo MA, Baeza M, Belmonte C (1995) CO_2 stimulation of the cornea: a comparison between human sensation and nerve activity in polymodal nociceptive afferents of the cat. Eur J NeuroSci 7:1154–1163

Chizh BA, Gohring M, Troster A, Quartey GK, Schmelz M, Koppert W (2007a) Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human volunteers. Br J Anaesth 98:246–254

Chizh BA, O'Donnell MB, Napolitano A, Wang J, Brooke AC, Aylott MC, Bullman JN, Gray EJ, Lai RY, Williams PM, Appleby JM (2007) The effects of the TRPV1 antagonist SB-705498 on TRPV1 receptor-mediated activity and inflammatory hyperalgesia in humans. Pain 132:132–141

Devor M, Seltzer Z (1999) Pathophysiology of injured nerve. In: Wall PD, Melzack R (eds) Textbook of pain. Churchill Livingstone, Edinburgh, pp 129–164

Dyck PJ, Peroutka S, Rask C, Burton E, Baker MK, Lehman KA, Gillen DA, Hokanson JL, Obrien PC (1997) Intradermal recombinant human nerve growth factor induces pressure allodynia and lowered heat pain threshold in humans. Neurology 48:501–505

Eisenbarth H, Rukwied R, Petersen M, Schmelz M (2004) Sensitization to bradykinin B1 and B2 receptor activation in UV-B irradiated human skin. Pain 110:197–204

Fairweather I, McGlone F, Reilly D, Rukwied R (2004) Controlled dermal cell damage as human in vivo model for localised pain and inflammation. Inflamm Res 53:118–123

Forster C, Magerl W, Beck A, Geisslinger G, Gall T, Brune K, Handwerker HO (1992) Differential effects of dipyrone, ibuprofen, and paracetamol on experimentally induced pain in man. Agents Actions 35:112–121

Gustorff B, Anzenhofer S, Sycha T, Lehr S, Kress HG (2004) The sunburn pain model: the stability of primary and secondary hyperalgesia over 10 hours in a crossover setting. Anesth Analg 98:173–177

Hamilton SG, Warburton J, Bhattacharjee A, Ward J, McMahon SB (2000) ATP in human skin elicits a dose-related pain response which is potentiated under conditions of hyperalgesia. Brain 123:1238–1246

Hoffmann RT, Schmelz M (1999) Time course of UVA- and UVB-induced inflammation and hyperalgesia in human skin. Eur J Pain 3:131–139

Hosogi M, Schmelz M, Miyachi Y, Ikoma A (2006) Bradykinin is a potent pruritogen in atopic dermatitis: a switch from pain to itch. Pain 126:16–23

Ikeda H, Heinke B, Ruscheweyh R, Sandkuhler J (2003) Synaptic plasticity in spinal lamina I projection neurons that mediate hyperalgesia. Science 299:1237–1240

Ikoma A, Fartasch M, Heyer G, Miyachi Y, Handwerker H, Schmelz M (2004) Painful stimuli evoke itch in patients with chronic pruritus: central sensitization for itch. Neurology 62:212–217

Kilo S, Schmelz M, Koltzenburg M, Handwerker HO (1994) Different patterns of hyperalgesia induced by experimental inflammations in human skin. Brain 117:385–396

Kilo S, Forster C, Geisslinger G, Brune K, Handwerker HO (1995) Inflammatory models of cutaneous hyperalgesia are sensitive to effects of ibuprofen in man. Pain 62:187–193

Klein T, Magerl W, Hopf HC, Sandkuhler J, Treede RD (2004) Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. J Neurosci 24:964–971

Klein T, Magerl W, Nickel U, Hopf HC, Sandkuhler J, Treede RD (2007) Effects of the NMDA-receptor antagonist ketamine on perceptual correlates of long-term potentiation within the nociceptive system. Neuropharmacology 52:655–661

Kohlloffel LU, Koltzenburg M, Handwerker HO (1991) A novel technique for the evaluation of mechanical pain and hyperalgesia. Pain 46:81–87

Koltzenburg M, Torebjörk HE, Wahren LK (1994) Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain. Brain 117:579–591

Koppert W, Dern SK, Sittl R, Albrecht S, Schuttler J, Schmelz M (2001) A new model of electrically evoked pain and hyperalgesia in human skin: the effects of intravenous alfentanil, S(+)-ketamine, and lidocaine. Anesthesiology 95:395–402

Koppert W, Brueckl V, Weidner C, Schmelz M (2004) Mechanically induced axon reflex and hyperalgesia in human UV-B burn are reduced by systemic lidocaine. Eur J Pain 8:237–244

Lotsch J, Angst MS (2003) The μ-opioid agonist remifentanil attenuates hyperalgesia evoked by blunt and punctuated stimuli with different potency: a pharmacological evaluation of the freeze lesion in humans. Pain 102:151–161

Miller CC, Hale P, Pentland AP (1994) Ultraviolet B injury increases prostaglandin synthesis through a tyrosine kinase-dependent pathway, Evidence for UVB-induced epidermal growth factor receptor activation. J Biol Chem 269:3529–3533

Mohammadian P, Hummel T, Loetsch J, Kobal G (1997) Bilateral hyperalgesia to chemical stimulation of the nasal mucosa following unilateral inflammation. Pain 73:407–412

Moiniche S, Dahl JB, Kehlet H (1993) Time course of primary and secondary hyperalgesia after heat injury to the skin. Br J Anaesth 71:201–205

Ochoa JL, Yarnitsky D (1993) Mechanical hyperalgesias in neuropathic pain patients: dynamic and static subtypes. Ann Neurol 33:465–472

Pedersen JL, Kehlet H (1998) Secondary hyperalgesia to heat stimuli after burn injury in man. Pain 76:377–384

Petersen KL, Rowbotham MC (1999) A new human experimental pain model: the heat/capsaicin sensitization model. NeuroReport 10:1511–1516

Petersen K, Schmelz M (2008) Human pain models: virtues and limitations. In: Castro-Lopez J, Raja SN, Schmelz M (eds) Pain 2008. An updated review. IASP Press, Seattle, pp 77–88

Petersen KL, Fields HL, Brennum J, Sandroni P, Rowbotham MC (2000) Capsaicin evoked pain and allodynia in post-herpetic neuralgia. Pain 88:125–133

Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B (2006) Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 123:231–243

Rukwied R, Meyer A, Schley M, Kluschina O, Schmelz M (2008) Nerve growth factor causes sustained nociceptor sensitization in human skin. Soc Neurosci Abstr 38:267.14

Sandkuhler J (2009) Models and mechanisms of hyperalgesia and allodynia. Physiol Rev 89:707–758

Schmelz M, Schmidt R, Bickel A, Handwerker HO, Torebjörk HE (1997) Differential sensitivity of mechanosensitive and -insensitive C-fibers in human skin to tonic pressure and capsaicin. Soc Neurosci Abstr 23(part 1):1004

Schmelz M, Schmidt R, Handwerker HO, Torebjörk HE (2000) Encoding of burning pain from capsaicin-treated human skin in two categories of unmyelinated nerve fibres. Brain 123:560–571

Schmidt R, Schmelz M, Torebjörk HE, Handwerker HO (2000) Mechano-insensitive nociceptors encode pain evoked by tonic pressure to human skin. Neurosci 98:793–800

Simone DA, Ngeow JVF, LaMotte RH (1985) Neurogenic spread of hyperalgesia after intracutaneous injection of capsaicin in human subjects. Soc Neurosci Abstr 11:123

Simone DA, Baumann TK, LaMotte RH (1989) Dose-dependent pain and mechanical hyperalgesia in humans after intradermal injection of capsaicin. Pain 38:99–107

Stein AT, Ufret-Vincenty CA, Hua L, Santana LF, Gordon SE (2006) Phosphoinositide 3-kinase binds to TRPV1 and mediates NGF-stimulated TRPV1 trafficking to the plasma membrane. J Gen Physiol 128:509–522

Tegeder I, Meier S, Burian M, Schmidt H, Geisslinger G, Lotsch J (2003) Peripheral opioid analgesia in experimental human pain models. Brain 126:1092–1102

Troster A, Sittl R, Singler B, Schmelz M, Schuttler J, Koppert W (2006) Modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by parecoxib in humans. Anesthesiology 105:1016–1023

Wasner G, Schattschneider J, Binder A, Baron R (2004) Topical menthol—a human model for cold pain by activation and sensitization of C nociceptors. Brain 127:1159–1171

Zhuang ZY, Xu H, Clapham DE, Ji RR (2004) Phosphatidylinositol 3-kinase activates ERK in primary sensory neurons and mediates inflammatory heat hyperalgesia through TRPV1 sensitization. J Neurosci 24:8300–8309