Scandinavian Journal of Pain 1 (2010) 203–204

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Editorial comment

# Electrically induced pain models: The benefit of "electric feel"

Kerstin Jung*, Lars Arendt-Nielsen

*Center for Sensory-Motor Interaction, Faculty of Medicine, Aalborg University, Aalborg, Denmark*

Quantitative, mechanism based evaluation of new and existing analgesics is needed for target validation and for selecting the most optimal patient population for clinical trials. Human experimental models of pain play an essential role in such proof-of-concept studies.

Chemical, thermal, mechanical and electrical experimental pain models applied to different tissues are valuable tools for the exploration of the pathogenesis of poorly understood symptoms in clinical pain and provide information about how specific compounds interact with such symptoms and hence underlying mechanisms. In addition to acute experimentally induced pain the same modalities when applied adequately to the skin can induce primary (peripheral sensitization) and/or secondary (central sensitization) hyperalgesia. An example of secondary hyperalgesia is pin-prick hyperalgesia surrounding the conditioning stimulus and allodynia to tactile stimulation.

Different model systems/mechanisms induce distinctly different pain symptoms and thereby approximate processes that may be applicable to clinical pain conditions. Therefore the availability of different experimental pain models to investigate different systems/mechanisms is a prerequisite for further development of mechanistic based drug evaluation, diagnoses and treatments.

However, before establishing a mechanism based experimental human pain model it is crucial to ensure that this type of somatosensory stimulation is adequately validated, reproducible and the mechanism of action sufficiently understood. If this is in place the model may act as pain bio-marker and provide the opportunity in healthy volunteers to provoke mechanisms which mimic one aspect of a complex clinical pain condition. Hence, the bio-marker can act as a proxy and hopefully show a predictive value when drug screening data are translated from animals via human volunteers into a selected clinical pain population.

Electrical stimulation used as pain model enjoys growing popularity for inducing a reliable and long-lasting experimentally induced hyperalgesia. Although electrical stimulation is not a natural stimulus as it bypasses the receptors it is very adequate and easy to use modality as the pulses are short lasting and can be repeated. Continuous electrical stimulation is thought to mimic ongoing activity as found in postoperative pain states and as part of neuropathic pain conditions and hence some of the evoked phenomena may have clinical relevance. Another finding that emphasizes the relevance of electrical stimulation as pain bio-marker was the discovery of a correlation between intense electrical high-frequency stimulation (HFS) and the induction of central sensitization. HFS can lead to long-term potentiation of nociception and pain (LTP). The significance of this information becomes clear when considering that LTP plays an important role in the induction and maintenance of central sensitization [1] which is known to play a key role in the induction and maintenance of chronic pain conditions [2]. The long-term sensitization is assumed to represent a different sub-set of mechanisms as compared with the more short lasting hyperalgesic reaction induced by a strong burst of nociception (e.g. evoked by i.d. capsaicin) [2,3].

However, lack of information about exact involved mechanisms often complicates the final transfer of certain experimental models to pharmacological testing in proof-of-concept studies. Hence, bringing to light specific mechanisms and conditions that are responsible for qualifying a pain model should present a main aim in this research field.

Recent studies have shown that the electrical stimulation protocol has apparently an eminent influence on the quality of pain that is induced [4,5]. Factors including electrode design, frequency, stimulation intensity and area have to be considered when evaluating possible effects. The electrode design seems to be closely correlated with the fiber type that is activated. Many studies focus on the selective activation of nociceptive specific nerve fibers. Mouraux et al. [6] demonstrated a selective activation of nociceptive Aδ-fibers by using intra-epidermal electrical stimulation. This specific electrode design led to a punctual stimulation of Aδ-fiber free nerve endings whereas an increase in spatial recruitment via the use of multiple stimulation electrode is assumed to result in a consistent C-fiber activation [7]. Besides the proven importance of electrode geometry the applied frequency gains in importance. Klein et al. [5] clearly illustrated a frequency dependence of electrically induced pain models. Painful electrical stimulation applied via the same electrode induced either long-term potentiation (LTP) or long-term depression (LTP) of pain perception depending on the applied stimulation frequency. Repeated application of high-frequency stimulation (HFS, 100 Hz) for a few seconds led to an enhancement of pain magnitude whereas low-frequency stimulation (LFS, 1 Hz for 15 min) resulted in a long-lasting depression of pain rating. However, recent studies challenge a simplistic fre-

DOI of refers to article:10.1016/j.sjpain.2010.08.002.
* Corresponding author.
*E-mail addresses:* kjung@hst.aau.dk (K. Jung), LAN@HST.AAU.DK (L. Arendt-Nielsen).

1877-8860/$ – see front matter 
doi:10.1016/j.sjpain.2010.09.006

quency dependence between LTP and LTD induction as LFS afferent stimulation was shown to be also sufficient for inducing LTP [8]. Hence, the activated nerve fiber type might have more impact on the induced model of synaptic plasticity than the applied stimulation frequency. Described studies support this assumption as LTP induction was always obtained after stimulation with C-fiber intensity. Consequently, an activation of nociceptive C-fibers seems necessary in order to facilitate LTP induction or other forms of central sensitization [9]. This fact emphasizes again the importance of electrode design which is thought to play a key role in activating specific nerve fibers.

In order to assess long-lasting changes within the nociceptive system the selection of adequate evaluation parameters is of particular importance. Besides psychophysical testing to assess specific somatosensory changes after conditioning stimulation sensory-evoked potentials (SEP) [4], blink-reflex (BR) [10] or the nociceptive withdrawal reflex (NWR) [11], are objective electrophysiological measurements which also have been used to assess central processing of nociception and sensitization.

In this issue, Dusch et al. [13] introduce a new experimental protocol of electrically induced pain to be used for profiling an analgesic compound (paracetamol). Different parameters including pain rating, axon reflex flare, and areas of pin-prick hyperalgesia and touch evoked allodynia were tested in order to evaluate the effect of orally administered paracetamol. Moreover, the applied cross over design should provide information about the variability of pain and hyperalgesia induced by this protocol. Therefore each subject received the electrical stimulation on two different days, separated by one week. Each examination day again included the application of two sets of electrical stimulation that were applied with a four hour time period in between.

Statistics show a significant correlation for pain rating, axon reflex flare, area of hyperalgesia and allodynia for the investigated four hour time interval when tested on the same day. When comparing performed sessions within a one week interval the authors could still show a correlation that was, however, less tight compared to the findings for the four hour interval. Even though these results confirm a well-defined reproducibility of the described stimulation protocol, the authors were less successful in proving the original hypothesis. Oral administration of paracetamol showed no significant effect on any of the included evaluation parameters when applying the described electrical stimulation paradigm. Consequently, questions arise if this stimulation protocol is adequate in order to judge analgesic and antihyperalgesic properties of certain drug classes.

In search of possible explanations, this paper points out the significant impact of pharmacological properties of a substance when choosing a suitable model for testing a specific analgesic. On one hand, the presented data confirms the aimed reproducibility, but at the same time the results also demand a modification in order to apply this model in screening of analgesics. The presented data makes clear that different substances and dosage might affect different pain models and hence it is important to have a platform with many models to differentiate the action.

Earlier published data from the same group [12] proved successfully the response of this model when testing the analgesic effect of i.v. alfentanil, ketamine and lidocaine. The described model enabled assessment of the time course of analgesic and antihyperalgesic effects with high temporal resolution and minimum tissue damage. When comparing both studies it becomes obvious that differences in analgesic drug classes and dosage forms apparently led to differing results within the same investigated model depending on which mechanisms are affected by the given compound.

Hence, the aim is to establish a platform of different models that are suitable for specific drug classes. Electrically evoked pain and secondary hyperalgesia provide a stable promising experimental model that is suitable to test analgesic and antihyperalgesic effects. Often based on the pre-clinical data a choice has to be made which human pain model should be used. In addition, previous knowledge from human trials will help selecting the best models for assessing the effect on specific mechanisms of a given compound. Furthermore, as shown by Dusch et al. [13], the validity (intra- and interindividual) of the model must be demonstrated in order to establish a predictive pain bio-marker. Detailed information about the specific model will help optimizing the drug development process by mechanisms based target validation which will allow a selection of patients based on the mechanisms that fit the putative mode of action of a particular drug.

The results from Dusch et al. [13] provide one tool which for selected drugs may be a potential useful tool in the understanding of mechanism of action of certain analgesic substances, which adds another building block in the translational bridge to novel drug testing. Unquestionably, detailed knowledge of mechanisms responsible for electrically induced pain induction is a prerequisite for qualifying this approach for future drug testing and how well it may predict responses in selected pain patient populations needs to be investigated.

## References

[1] Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci 2003;26:696–705.
[2] Sandkuhler J. Learning and memory in pain pathways. Pain 2000;88:113–8.
[3] Willis WD. Long-term potentiation in spinothalamic neurons. Brain Res Rev 2002;40:202–14.
[4] Jung K, Rottmann S, Ellrich J. Long-term depression of spinal nociception and pain in man: influence of varying stimulation parameters. Eur J Pain 2009;13:161–70.
[5] Klein T, Magerl W, Hopf HC, Sandkuhler J, Treede RD. Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. J Neurosci 2004;24:964–71.
[6] Mouraux A, Iannetti GD, Plaghki L. Low intensity intra-epidermal electrical stimulation can activate a delta-nociceptors selectively. Pain 2010;150:199–207.
[7] Ostsuru N, Inui K, Yamashiro K, Miyazaki T, Ohsawa I, Takeshima Y, Kakigi R. Selective stimulation of C fibers by an intra-epidermal needle electrode in humans. Open Pain J 2009;2:53–6.
[8] Ikeda H, Stark J, Fischer H, Wagner M, Drdla R, Jager T, Sandkuhler J. Synaptic amplifier of inflammatory pain in the spinal dorsal horn. Science 2006;312:1659–62.
[9] Liu X, Sandkuhler J. Characterization of long-term potentiation of C-fiber-evoked potentials in spinal dorsal horn of adult rat: essential role of NK1 and NK2 receptors. J Neurophysiol 1997;78:1973–82.
[10] Ellrich J, Schorr A. Low-frequency stimulation of trigeminal afferents induces long-term depression of human sensory processing. Brain Res 2004;996:255–8.
[11] Andersen OK, Spaich EG, Madeleine P, Arendt-Nielsen L. Gradual enlargement of human withdrawal reflex receptive fields following repetitive painful stimulation. Brain Res 2005;1042:194–204.
[12] Koppert W, Dern SK, Sittl R, Albrecht S, Schuttler J, Schmelz M. A new model of electrically evoked pain and hyperalgesia in human skin – the effects of intravenous alfentanil, S(+)-ketamine, and lidocaine. Anesthesiology 2001;95:395–402.
[13] Dusch M, Namer B, Strupf M, Schley M, Rukwied R, Hägglöf B, Schmelz M, Koppert W. Cross-over evaluation of electrically induced pain and hyperalgesia. Scand J Pain 2010;1:205–10.