Predictivity of Pain Models

Karl-Heinz Konopka, PhD
Associate Scientific Director Translational & Development Pharmacology *

* Disclaimer: This is not an Astellas presentation
Synopsis

- **Introduction into Pain:**
  - Definition
  - Introduction into Neuropathic Pain
  - Introduction into Peripheral Neuropathic Pain in Animals
  - Human Pain Models

- **Quantitative Sensory Testing**
  - Introduction
  - Concept
  - Clinical relevance

- **Clinical vs. Experimental Pain**

- **Prediction of Clinical Analgesia by Human Experimental Pain Models**

- **Summary and Outlook**
Definitions

IASP (International Association for the Study of Pain)

- **Pain:** An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

- **Allodynia:** Pain due to a stimulus that does not normally provoke pain.

- **Hyperalgesia:** Increased pain from a stimulus that normally provokes pain.
The Pain Pathway
Basic pain research allowed the development of theories regarding pain mechanisms:
- Gate control theory
- Concept of neuroplasticity
- Cellular and molecular mechanisms of peripheral and central sensitization

These developments have been translated into clinical practice:
- Multimodal approaches to pain relief
- Earlier or preemptive provision of analgesia
- Extended postoperative pain management

However:
- There is a lack of success in translating the growing body of basic science data obtained using animal models as well as human pain models into new, effective and safe clinical analgesics
Introduction: Neuropathic pain

- The International Association for the Study of Pain (IASP) defined neuropathic pain as pain caused by a lesion or disease of the somatosensory system.

- Neuropathic pain has traditionally been classified based on its underlying aetiology.

- Until now, neuropathic pain classification according to the aetiology has been the basis for its pharmacological treatment, including tricyclic antidepressants, anticonvulsants and opioids.

- However, improvement of pain complaints of more than 50% is achieved in less than one-third of neuropathic pain patients studied.

- A way to provide more insight in the distinct underlying mechanisms for the different types of neuropathic pain patients is to investigate symptoms and sensory signs in greater detail.
Neuropathic Pain Patients

Prof. Peter McNaughton, FMedSci King’s College London
Models of neuropathic pain – peripheral nerve injury model in rodents

- **Partial sciatic nerve ligation** (PSL or Seltzer model):
  - Exhibit signs of hyperalgesia and allodynia to mechanical and thermal-noxious stimuli within hours post surgery

- **Chronic constriction model** (CCI or Bennett model):
  - Hyperalgesia and allodynia due to noxious thermal and mechanical stimuli is detectable

- **L5/L6 spinal nerve ligation** (SNL or Chung model):
  - Allodynia and hyperalgesia develop quickly after ligation
Models of neuropathic pain – peripheral nerve injury model in rodents

- Bennett (CCI), Seltzer (PSL) and Chung (SNL) are the three most widely used peripheral neuropathy models:

<table>
<thead>
<tr>
<th>Model</th>
<th>Spontaneous pain</th>
<th>Autotomy</th>
<th>Mechanical allodynia</th>
<th>Cold allodynia</th>
<th>Thermal hyperalgesia</th>
<th>Mechanical hyperalgesia</th>
<th>Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCI</td>
<td>++ +</td>
<td>+</td>
<td>+</td>
<td>++ +</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>PSL</td>
<td>++ +</td>
<td>±</td>
<td>+</td>
<td>+ +</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SNL</td>
<td>+ + +</td>
<td>-</td>
<td>+ + +</td>
<td>+ +</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

CCI, chronic constriction injury model [80,81]; PSL, partial sciatic nerve ligation model [62]; SNL, L5/L6 spinal nerve ligation model [63]. The onset of pain for all three models is within hours to 1 day. The duration of pain is over weeks, but may vary somewhat in different studies and among tests [62,80,81,83,84].

- Which model is most predictive for efficacy in humans?
  - No consistent data available, but most Labs use data from two peripheral nerve injury models to predict efficacy in humans
  - No consistent data available for frequency of onset of sensory/behavioural changes and how novel compounds been evaluated (blind, double blind...)

Wang et al., 2003 Advanced Drug Delivery Reviews 55, 949–965
Neuropathic pain models and outcome measures

- Spontaneous pain vs. evoked pain
  - Outcome measure reflect reflex hypersensitivity and not pain or co-morbidities
  - Neuropathic pain in humans is heterogenic in onset and neuropathology

<table>
<thead>
<tr>
<th>Outcome measures:</th>
<th>Animal</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evoked pain</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Spontaneous pain</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Paroxysmal pain</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Translation from preclinical models to the clinic

- Use same testing methods and biomarkers between animals and humans
- Increase chance of success by aligning preclinical and clinical mechanistic models
- Allows targeting of pain mechanisms for wanted effects

First clue that the latest medical breakthrough isn’t quite there yet.
Potential targets for new drug development

- Adenosine receptors
- Cannabinoid receptors (CB1,CB2)
- Chemokines
- Cytokines
- Nerve growth factor
- Glutamate receptors
- Neurokinin receptors
- NMDA receptors
- Potassium channels
- Purinergic P2 receptors
- Transient receptor potential channels
- Voltage-gated calcium
- Sodium channels

Few truly new drugs have been brought into clinical practice!

Drugs that have been introduced are either analgesics of the same class as others already in clinical use or have been derived from clinical observation in other settings (e.g., gabapentinoids, ketamine)
Pain is a complex multi-dimensional experience

Clinical scientists try to squeeze the complex pain experience into a simplistic measure (Visual Analogue Scale (VAS)) where the multidimensional aspect of pain is reduced to one dimension.
Human experimental models could provide a missing step

“I think you should be more explicit here in step two.”

from *What's so Funny about Science?* by Sidney Harris (1977)
Human experimental pain models can be supportive in understanding the pain mechanisms and appear to be ideally suited to test analgesic compounds.

The challenge is to match specific treatments to different pain-generating mechanisms and hence reach a pain treatment tailored to each individual patient.

Experimental pain models offer the possibility to explore the pain system under controlled settings. Standardized stimuli of different modalities (i.e., mechanical, thermal, electrical, or chemical) can be applied to the skin, muscles, and viscera for a differentiated and comprehensive assessment of various pain pathways and mechanisms.

The value of human experimental pain models is to link animal and clinical pain studies, providing new possibilities for designing successful clinical trials.
Frequently used experimental pain models

<table>
<thead>
<tr>
<th>Experimental pain condition</th>
<th>Experimental stimulus/model</th>
<th>Stimulation site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical (punctate, nasal)</td>
<td>Gaseous CO₂ stimulus</td>
<td>Nasal mucosa</td>
</tr>
<tr>
<td>Chemical hyperalgesia</td>
<td>Capsaicin</td>
<td>Skin (topical, intracutaneous)</td>
</tr>
<tr>
<td>Chemical hyperalgesia (visceral)</td>
<td>Hypertonic saline</td>
<td>Skin (intracutaneous, intramuscular)</td>
</tr>
<tr>
<td>Chemical hyperalgesia + Cold (contact)</td>
<td>Hydrochloric acid</td>
<td>Gastrointestinal tract (oesophagus, gut)</td>
</tr>
<tr>
<td>Chemical hyperalgesia + Heat (contact)</td>
<td>Menthol + Medoc-TSA (cold)</td>
<td>Skin (topical)</td>
</tr>
<tr>
<td>Chemical hyperalgesia + Pressure (blunt)</td>
<td>Capsaicin + Medoc-TSA (heat)</td>
<td>Skin (topical, intracutaneous)</td>
</tr>
<tr>
<td>Chemical hyperalgesia + Pressure (punctate)</td>
<td>Glutamate injection + Algorometry</td>
<td>Intramuscular injection (masseter, splenius)</td>
</tr>
<tr>
<td>Cold thermode (contact)</td>
<td>Capsaicin + von Frey</td>
<td>Skin (topical, intracutaneous)</td>
</tr>
<tr>
<td>Cold water (contact)</td>
<td>Capsaicin + Pinprick</td>
<td>Skin (topical, intracutaneous)</td>
</tr>
<tr>
<td>Electrical hyperalgesia + Pressure (punctate)</td>
<td>Hyperpotic saline + Pinprick</td>
<td>Intracutaneous, intramuscular injection (masseter, splenius)</td>
</tr>
<tr>
<td>Electricity</td>
<td>Medoc-TSA (cold)</td>
<td>Skin</td>
</tr>
<tr>
<td>Heat (contact)</td>
<td>Ice Water</td>
<td>Skin</td>
</tr>
<tr>
<td>Heat (punctate)</td>
<td>Neumeter + Pinprick</td>
<td>Skin (topical, intracutaneous), dental pulp, earlobe, intramuscular (muscle RIII)</td>
</tr>
<tr>
<td>Heat (visceral)</td>
<td>Neumeter</td>
<td>Skin (topical, intracutaneous), dental pulp, earlobe, intramuscular (muscle RIII)</td>
</tr>
<tr>
<td>Inflammatory hyperalgesia</td>
<td>Medoc-TSA (heat)</td>
<td>Skin (topical)</td>
</tr>
<tr>
<td>Inflammatory hyperalgesia (punctate, nasal)</td>
<td>Laser</td>
<td>Skin (topical)</td>
</tr>
<tr>
<td>Inflammatory hyperalgesia + Electricality</td>
<td>Balloon heat</td>
<td>Gastrointestinal tract (oesophagus, gut)</td>
</tr>
<tr>
<td>Inflammatory hyperalgesia + Heat (contact)</td>
<td>Freeze lesion</td>
<td>Skin (topical)</td>
</tr>
<tr>
<td>Inflammatory hyperalgesia + Pressure (punctate)</td>
<td>Freeze lesion + Electrical stimulus</td>
<td>Skin (topical)</td>
</tr>
<tr>
<td>Ischaemic pain</td>
<td>Freeze lesion + Medoc-TSA (Heat)</td>
<td>Skin (topical)</td>
</tr>
<tr>
<td>Mechanical hyperalgesia + Pressure (punctate)</td>
<td>Tourniquet</td>
<td>Arm, forearm, thigh, calf, finger, toe, etc.</td>
</tr>
<tr>
<td>Mechanical hyperalgesia + Pressure (punctate)</td>
<td>Repeated Pinprick</td>
<td>Skin (topical)</td>
</tr>
<tr>
<td>Muscle ache</td>
<td>Delayed onset muscle soreness</td>
<td>Jaw muscle</td>
</tr>
<tr>
<td>Pressure (blunt)</td>
<td>Algorometry</td>
<td>Interdigital web, phalanx, finger pulp, extensor digitor</td>
</tr>
<tr>
<td>Pressure (punctate)</td>
<td>Pinprick</td>
<td>Skin (topical)</td>
</tr>
<tr>
<td>Pressure (visceral)</td>
<td>Balloon distension</td>
<td>Gastrointestinal tract (oesophagus, gut)</td>
</tr>
<tr>
<td>Thermal hyperalgesia</td>
<td>Heat lesion</td>
<td>Skin (topical)</td>
</tr>
<tr>
<td>Thermal hyperalgesia + Heat (contact)</td>
<td>Heat lesion + Medoc-TSA (heat)</td>
<td>Skin (topical)</td>
</tr>
<tr>
<td>Thermal hyperalgesia + Pressure (punctate)</td>
<td>Heat lesion + Pinprick</td>
<td>Skin (topical)</td>
</tr>
<tr>
<td>U/V-B hyperalgesia + Heat (contact)</td>
<td>U/V-B radiation + Medoc-TSA (Heat)</td>
<td>Skin (topical)</td>
</tr>
<tr>
<td>U/V-B hyperalgesia + Pressure (punctate)</td>
<td>U/V-B radiation + Pinprick</td>
<td>Skin (topical)</td>
</tr>
</tbody>
</table>
Main components of experimental pain
Human Experimental Pain

- Several models of human experimental pain stimulation exist.
  - Important experiments related to pathophysiological changes in the pain system are induction of hyperalgesia and allodynia. Such procedures may be helpful in the evaluation of various drug effects on peripheral and central mechanisms.

- Mimicking aspects of clinical pain condition, but can not reflect the full multidimensionality of a disease.
  - In case of neuropathic pain the most relevant aspects are ongoing pain and sensory abnormalities such as hyperalgesia and allodynia.
Neuropathic Pain Assessments

Neuropathic Symptoms Tool:
- scales
- inventory
- questionnaires

Pain

Spontaneous Pain
- Continuous
- Intermittent

Evoked Pain
- Allodynia
- Hyperalgesia

Mechanical
- Static \ Dynamic

Thermal
- Cold \ Warm

Further Bedside Tests: Neuropathic Symptoms Tool:
- QST: Detection of sensory loss and sensory gain

Bedside Tests:
- Allows to identify and qualify Neuropathic Pain

Modified from Woolf et al., 1999
Quantitative Sensory Testing (QST)

- Developed as part of the nationwide multicenter German Research Network on Neuropathic Pain (DFNS) in healthy volunteers.
- Different clinical signs and symptoms reflect different pathophysiological mechanisms.
- The QST battery includes robust and validated short form tests representing measures of all relevant submodalities of the somatosensory system.
- 7 tests measuring 13 parameters, contain both thermal and mechanical stimuli (takes about 1h).
- QST enables us to characterise the somatosensory phenotype of Neuropathic Pain in patients more precisely.
How does Quantitative Sensory Testing differ from current clinical practice?

- Offers a standardized approach to sensory testing and evaluates all pain relevant sensory fibers
- Evaluates and quantifies both sensory loss and sensory gain
- Does not rely on non-affected side for reference values
- Quantitative measures of symptoms and signs offer an opportunity to improve our measurement of neuropathic pain

Postherpetic Neuralgia

\[ Z = \frac{(\text{raw score (patient)} - \text{mean (healthy controls)})}{\text{SD (healthy controls)}} \]

Z-score profiles at the affected side and contralateral side in neuropathic pain patients

Diagnostic consequence of using either the contralateral side or normative data from healthy volunteers

<table>
<thead>
<tr>
<th>observation affected side</th>
<th>observation contralateral side</th>
<th>clinical result using contralateral side as reference</th>
<th>clinical result using healthy volunteers as reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>-</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0</td>
<td>+</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>-</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>--</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Clinical versus experimental pain

Schematic overview of factors influencing a patient’s perception of pain in the clinic (top) and illustration of concepts in experimental pain (bottom)
The overall prediction of analgesic efficacy or failure of a drug correlated well between experimental and clinical settings.

We hypothesized that if an analgesic drug was effective in an experimental pain model and also a specific clinical pain condition, then that model might be predictive for that particular condition and should be selected for development as an analgesic for that condition.

The validity of the prediction increases with an increase in the numbers of analgesic drug classes for which this agreement was shown.

Only five clinical pain conditions were correctly predicted by seven different pain models for at least three different drugs. Most of these models combine a sensitization method.
Clinical pain conditions predicted by an experimental pain condition
Summary and Outlook

- Experimental methods to evoke and assess pain under controlled circumstances are advantageous and offer a unique opportunity to investigate analgesic effects on different pain modalities arising from different tissues as well as peripheral and central pain mechanism.

- The disadvantages of experimental models are the short lasting acute stimuli and hence the limited psychological involvement. The experimental stimuli may therefore not mimic clinical pain sufficiently as pain experienced and reported by healthy volunteers is different from clinical pain.

- Sensitization, a hallmark of clinical pain, can be evoked experimentally in healthy volunteers to mimic pathological conditions such as allodynia and hyperalgesia.

- A better understand of clinical pain and its evaluation might improve the predictability of human pain models.

- By analyzing how drugs work in experimental and clinical settings, it was shown that different sets of experimental pain models, rather than single models, may be best suited to provide predictive studies in analgesic drug development.

- Analgesic effects on experimental and on clinical pain may serve as a basis to identify human pain models that bridge basic science with clinical pain research.

- A cross-validation of human experimental models with clinical pain is needed to further increase the predictability of human pain models.