Measurement of nociception in experimental studies

1st Vienna Pain Day, 1-2 July 2017

Prof. C. Spadavecchia
Anaesthesiology and Pain Therapy Section
Department of Clinical Veterinary Medicine
Vetsuisse Faculty, University of Bern

Issues in Veterinary Pain Research

Pain Assessment in research settings

- Physiological parameters
  - HR, HRV, BP, cortisol, b-endorphines

- Behavioural based scoring systems
  - Facial pain scales, DIVAS, HCPI

- Nociceptive thresholds determination
  - Quantitative Sensory Testing methods

Nociceptive thresholds
Nociception

from the Latin "nocere" (to harm)

"The neural process of encoding noxious stimuli"

*Note:* Consequences of encoding may be autonomic (e.g. elevated blood pressure) or behavioral (motor withdrawal reflex or more complex nocifensive behavior).
Pain sensation is not necessarily implied.

Nociception has an important warning function

---

Quantitative Sensory Testing (QST)

- Assessment of peripheral nociceptive sensory function
- Central sensitization and integration
- Multimodal/multi-tissue approach

- Basic mechanistic studies in healthy subjects
- Clinical studies for diagnostic and monitoring purposes
- Pharmacological studies to evaluate analgesic efficacy

Arendt-Nielsen et al. 2009

Psychophysical testing
- Sensory stimulus is an objective physical event
- Response is the subjective conscious report/reaction

Neurophysiological testing
- Sensory stimulus is an objective physical event
- Response is the evoked neurophysiological response
Psychophysical QST

- Outcome is a (nocifensive) behavioural reaction
- The reaction has to be interpreted
- Thresholds/reaction times are measured
- Pharmacological threshold changes are detected
- Low threshold mechano- and thermoreceptors are activated
- Influenced by drugs altering behaviour
- Learning effect can occur

Psychophysical QST: thermal threshold

- Threshold determination: heat and cold
- Methods: thermode, Peltier cell, radiant heat, immersion
- Skin properties and contact surface
- Thermal stimulation is always progressive: reaction time
- Heating slope
  - 1° C/s: C fibers
  - 6.5° C/s: Aδ fibers
- Cut off values

Psychophysical QST: mechanical threshold

- Behavioural response to heating: determinants

---

Benoist et al. 2008
Psychophysical QST: mechanical threshold

- Threshold determination
  - Von Frey filaments
  - Algometry

- Methods
  - Hand-held or fixed actuator
  - Manual or computer-recorded

- Rate of force increase
- Stimulating surface

Psychophysical QST: electrical threshold

- Stimulation of nociceptors is elicited by pressure
  - $p = \frac{F}{A}$

- Pressure depends on the stimulation surface
- Force is independent from the stimulation surface

Psychophysical QST: electrical threshold

- Direct versus alternating current
- Constant current/voltage stimulation
- Electrodes impedance/resistance

- Ohm's law: $I = \frac{V}{R}$

RESEARCH PAPER

Determination of the minimum alveolar concentration of isoflurane in Shetland ponies using constant current or constant voltage electrical stimulation

Constant current surface electrode stimulations were the most repeatable and gave clearer responses.
Neurophysiological QST

- Outcome is a recorded evoked reaction
- The reaction can be quantified
- Thresholds and stimulus-response curves can be determined
- Pharmacological modulation can be detected
- Less influenced by drugs altering behaviour
- Low threshold mechano- and thermoreceptors are not activated if electrical stimulation is used

Nociceptive Withdrawal Reflex (NWR)

The NWR: Nociceptive Withdrawal Reflex

Stimulus-response function

Temporal summation: biomarker for neurogenic pain

The Veterinary Journal

Nociceptive trigeminal reflexes in non-sedated horses

K.O. Veres-Nyelki, M., Leitlh, C., Spuler, J.

Contents late available at ScienceDirect
Neurophysiological QST

Conditioned Pain Modulation (CPM)

Extent of threshold change during application of a conditioning noxious stimulus

28. Juni 2017

QST in pre- and para-clinical drug testing

- Species-specific approach
- Focus on antinociceptive activity
- New and existing drugs
- Insight into mechanisms of action
- Investigation of several doses and infusion rates
- Support from/for clinical studies

Aim= Optimization of clinical veterinary practice

QST in clinical pain syndromes

- Characterization of spontaneously occurring pain syndromes
- Understanding of involved processing mechanisms
- Diagnosis of peripheral (and central) sensitization
- Mechanisms-based approach to therapy
- Treatment follow up

Aim= complementary tool for a through understanding of clinical pain conditions

Future development

- Improve quality and standardization of QST methods for nociceptive threshold determination
- Explore mechanisms of nociceptive processing involved in threshold determination methods to increase specificity
- Develop multi-tissue nociceptive markers and experimental sensitization methods