Nociceptive processing: An option for targeting treatment?

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TOPICS

> Conceptual framework
> Phenotyping for nociceptive processes
> Current evidence on mechanism-based treatments
> Prospects

Limited to pharmacological treatments
Reasons for individualized pain treatment

Response to pain medications:
- Is typically low
- Varies enormously
- Is unpredictable

Trial-and-error is associated with:
- Prolonged times to identify the right medication
- Exposure to side effects and complications with uncertain benefits
Predictors of drug efficacy

Selection of treatment

Lower NNT
Higher NNH
Mechanism-based approach - Rationale

> Medication management is currently targeted to diagnostic categories (LBP, PHN, etc.)

> Within the same diagnostic categories, different mechanisms are involved, e.g. for neuropathic pain:
  - Ectopic nerve activity (enhanced expression of voltage-gated Na⁺ channels, TRPV1, etc.)
  - Central sensitization (enhanced neuron excitability, disinhibition, neuro-inflammation, etc.)
  - Etc.
Different mechanisms are involved in different patients with the same diagnosis.

Medications work only in part of these mechanisms.

1. Identification of underlying mechanisms
2. Medication targeting mechanisms
3. Lower NNT
Challenges

Methods to study directly nociceptive processes in humans are

> Limited in scope
> Not for clinical practice

We have to use surrogate measures / biomarkers

Courtesy L. Arendt-Nielsen
What is a biomarker?

> A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions

Robb et al, JAMA 2016

> Biomarkers are not clinical endpoints

Any useful biomarker must eventually show a link to a relevant clinical endpoint
Quantitative sensory tests

> Application of a stimulus
> Response (subjective, electrophysiological, etc.)

> Can be used bed-side
> Are reliable

> Have been used extensively in research
> Have some clinical use, particularly in neuropathic pain

> Their validity for nociceptive processes is unclear due to lack of reference standards
Are QST all the same?

- Factor analysis in 272 pain-free subjects
- 5 factors cumulatively explained 94% of the variance: pressure, heat, cold, electrical stimulation and reflex receptive fields

Responses to different modalities represent different dimensions of pain perception

Neziri et al, Pain 2011

The correlation between the 5 factors was near 0
Mechanisms that can be assessed in humans

> Sensitization
  – QST at non-injured areas → Widespread sensitization
  – QST at injured areas → Nociceptor sensitization / Central sensitization

> Spinal cord nociceptive hypersensitivity (NWR)

> Temporal summation (pain threshold, NWR)

> Receptive fields (reflex receptive fields)

> Gain/loss of nerve fiber function

> Endogenous modulation (CPM)

> …
Phenotyping patients with neuropathic pain

- 902 Patients with different types of neuropathic pain
- Validation on another set of 233 patients
- Etiologies: polyneuropathy, peripheral nerve injury, post-herpetic neuralgia and radiculopathy

- 13 different mechanical and thermal QST
- Z scores calculated based on previous studies on healthy subjects as reference values
  - Z scores >0 = gain in function
  - Z scores <0 = loss in function

Baron et al, Pain 2017
Clusters:
1. Sensory loss (loss of fiber function; ectopic activity)
2. Thermal hyperalgesia (mostly peripheral sensitization; spontaneous activity in surviving nociceptors)
3. Mechanical hyperalgesia (mostly central sensitization; possibly ectopic activity in nociceptors)

- All 3 clusters distributed across all 4 etiologies
- Some quantitative differences

What next?

Baron et al, Pain 2017
Nociceptive processes

Phenotype

Outcome

Medication

Speculative

Open issues

- Altered CPM → Antidepressants? GABA-agonists?
- Heat hyperalgesia / irritable nociceptor → Na-channel blockers? Topical capsaicin?
- …?
Alteration of endogenous modulation

- Placebo-controlled

Efficacy of duloxetine in diabetic polyneuropathy

- 30 patients
- No data on sensitivity-specificity-LR
- Other QST not predictive

Yarnitsky et al, Pain 2012
QST
Multiple tests

Efficacy of capsaicin patch 8% in peripheral NP

Mainka et al, EJP 2016

- Cold and pinprick hyperalgesia: prediction of responders with 100% specificity and 70% sensitivity
- Many analyses, 20 patients, no control group, not powered on sensitivity and specificity, likely large CI (no data)
Pain after 0.1% topical capsaicin (hyperactive nociceptor)

Efficacy of topical clonidine in diabetic polyneuropathy

- No data on sensitivity-specificity-LR
- Other QST not predictive

Campbell et al, Pain 2012
Mechanical and/or heat hyperalgesia (irritable nociceptor)

Efficacy of oral oxcarbazepine in neuropathic pain

NNT for 50% pain relief:
- 3.9 (95% CI 2.3-12) irritable nociceptor
- 13 (95% CI 5.3-1) non-irritable nociceptor

Demant et al
Pain 2014
Phenotyping for neuropathic pain

- Retrospective, from 7 placebo-controlled clinical trials
- Similar design and outcome recordings
- 4 antidepressants and 4 anticonvulsants
- Imipramine and pregabalin: better effect in patients with gain of sensory function
- Pregabalin: better effect with preserved large fiber function
- No phenotype-specific effects for venlafaxine, escitalopram, oxcarbazepine, valproic acid, levetiracetam, or St. John’s wort

- Overall, doubtful usefulness of phenotyping

Holbech et al, Pain 2014
Predicting medication effect in low back pain

- 50 patients with chronic low back pain
- Imipramine
- Oxycodone
- Clobazam
- Placebo-controlled, crossover
- 2h observation after administration
- Extensive QST protocol for potential predictors
- Pharmacogenetics

Siegenthaler et al, BMC Pharmacol Toxicol 2015

(Study protocol)
Results

Oxycodone and clobazam
> Superior to placebo for pain relief
> No QST predicted the analgesic effect

Imipramine
> Overall not better than placebo
> Better than placebo in patients with heat or cold hyperalgesia

Schliessbach et al, unpublished
Imipramine

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<td>Overall</td>
<td>98</td>
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<td>Baseline HPTT (leg) at limit</td>
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<td>0.63 (0.14 to 1.12)</td>
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<td>-0.55 (-1.14 to 0.04)</td>
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<td>0.57 (0.14 to 1)</td>
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<td>45</td>
<td>-0.51 (-1.08 to 0.06)</td>
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Schliessbach et al, unpublished
TAKE-HOME MESSAGES (I)

> Pharmacological treatment targeted to nociceptive processes has the potential to improve pain management
> Phenotyping patients to identify nociceptive processes at individual level is challenging
> Recent research is encouraging – we see some signal
> The most consistent finding is a better response to medications in patients with thermal hyperalgesia
TAKE-HOME MESSAGES (II)

Limitations:

> Inconsistent findings regarding predictive value of QST
> No QST found to be clearly predictive across studies
> Sensitivity, specificity and likelihood ratio either not analyzed or shown to be low

> Targeting nociceptive processes at individual level is still a research aim, not yet an achievement
> Search for more mechanistic biomarkers is a relevant aim of future research
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