New Millennium

• A - Introduction
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• E – Cognitive Modulations of Pain
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Clinical Pain Relief Service

Acute Pain

Chronic Pain

Cancer Pain
Enhanced Pain Management

Pronociceptive targets

Antinociceptive targets

↑ Inhibition

↓ Excitation
Neural Influences on Pain and Sensory Processing

Facilitation
- Substance P
- Glutamate and EAA
- Serotonin (5HT$_{2a, 3a}$)
- Nerve growth factor
- CCK

Inhibition
- Descending anti-nociceptive pathways
  - Norepinephrine-serotonin (5HT$_{1a,b}$), dopamine
  - Opioids
  - GABA
  - Cannabinoids
  - Adenosine

(Phillips K. Best Pract Res Clin Rheumatol 2011;25(2):141-54)
A - Introduction

• One in six New Zealanders (16.9%) suffer from chronic pain - data from the 2006/07 New Zealand Health Survey (Dominick C. NZ Med J 2011;124(1337):63-76)

• 48% used some form of medical treatment

• Prevalence increased with age from 8.6% to 28.1%

• Chronic pain represents a major health issue in New Zealand
B. Pain Conduction

Ligands with non-neuronal sources
- Acetylcholine
- ATP
- Prostaglandin E
- Opioids
- Adenosine
- Glutamate
- Bradykinin, histamine
- Serotonin

Ligands in nociceptors:
- Substance P
- ATP
- Neuropeptide Y
- Cholecystokinin
- Bombesin
- Opioids
- Adenosine
- Glutamate
- Somatostatin

Volume transmission
Autoreception
Paracrine reception

Receptors associated with nociceptors
- ATP, neurokinin 1
- Neuropeptide Y, acetylcholine
- Prostaglandin E, cholecystokinin
- Serotonin, bombesin
- Bradykinin, histamine
- Opioids
- Adenosine
- GABA$_A$, GABA$_B$
- Somatostatin
- Adrenaline
- Glutamate
- Capsaicin
- Angiotensin II
Interactions between different excitatory and inhibitory systems in the spinal cord

Lancet
1999;353:1613
The Somatosensory System

Frontal Cortex

Descending Paths

Descending Facilitatory

Gray Matter

Periaqueductal Gray Matter

Glial Cell Activation

Peripheral Receptor Activation

Somatosensory cortex

Thalamus

Hypothalamus

Ascending Tracts

Midbrain

Medulla

Dorsal Horn

Spinal Cord
<table>
<thead>
<tr>
<th>Na Channels In PSN</th>
<th>TTX sensitivity</th>
<th>Normal DRG Expressn</th>
<th>Growth factor Dependence</th>
<th>Inflammation</th>
<th>Neuro-pathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNS2/NaN NaV 1.9</td>
<td>Resistant</td>
<td>Yes</td>
<td>GDNF</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>III NaV 1.4</td>
<td>Sensitive</td>
<td>No</td>
<td>?</td>
<td>X</td>
<td>↑</td>
</tr>
<tr>
<td>SNS/PN3 NaV 1.8</td>
<td>Resistant</td>
<td>Yes</td>
<td>NGF</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
C. Peripheral and Central Sensitisation - Neuroglial cells

Verkhratsky A. Neurochem Int 2010;57(4):332-43
Central Sensitisation

- Neurone
- Microglia
- Fractalkine

Normally non-painful stimuli become painful

Proinflammatory cytokines

Sub P, EAA, NO, PG, Reactive O2

Central Sensitisation
D. Brain Imaging
Pain Imaging

PET
- rCBF
  - Resting state
  - Neuropathic pain (heat allodynia)

fMRI
- rCBF
  - No radiation/stimulus dependent
  - Visceral Pain
  - Imaging opioid receptors, neurotransmitters
Graphic depiction of brain regions receiving nociceptive input and activated in MRI studies.
Understanding chronic inflammatory and neuropathic pain
(Anals NY Acad Sc 2012 May:30-44) Chronic pain gives reduced gray matter volume; it reshapes the brain.

Sensory-related areas: volume decreases in areas correlated with increased mechanical sensitivity.

Affect-related areas: volume decreases in regions with the onset of anxiety-like behaviour.
Psychological Effects

- Sleep Disturbance
- Avoidance of Physical Effort
- Physical Deconditioning
- Pain
- Neuroendocrine Perturbations
- Health Beliefs/Mood Disorder

Cur Opin Anaesth 2001;14:536
activation of such as the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and to the anterior cingulate cortex (ACC)

Jensen KB Neurosci Lett 2012;520(2):156-64
Physical pain

Social distress

Activate Anterior Cingulate Cortex

Common neurobiological pathways
Evaluation of CBT in FM patients
Jensen KB Neurosci Lett 2012;520(2):156-64

↑ pain-evoked brain activity in the left lateral prefrontal cortex in CBT group after treatment, compared to controls

↑ connectivity between the left lateral prefrontal cortex and the thalamus in CBT group, compared to controls
Mindfulness meditation significantly reduced pain (Zeidan F. Neurosci Lett 2012;520(2):165-73)

noxious heat, meditation significantly lower level afferent processing in primary somatosensory cortex (SI)

meditation-related pain intensity reductions were associated with greater activity in rostral anterior cingulate cortex (rACC), an area involved in cognitive control

Greater orbitofrontal cortex (OFC) activity was associated with greater decreases in pain unpleasantness ratings. Moreover, thalamic (ThI) deactivation was associated with reductions in pain unpleasantness
Cortical reorganisation of sensory homunculus
F- Genetics and Pain

Knock-Out Mice + Gene Array Studies
G. New Drugs - Tapentadol

MOR-NRI open-chain structure

- strong μ-opioid receptor agonism
- noradrenaline reuptake inhibition

- undergoes phase II metabolism (glucuronidation)

- controlled substance with reduced gastrointestinal adverse effects

- potency/efficacy comparable to strong opioids

- no analgesically active metabolite
Opioid Antagonists

Methylnaltrexone
does not pass blood–brain barrier; analgesic effect of opioids is unaffected; 0.15 mg/kg SC

Oral Oxycodone with Naloxone (Targin) in ratio of 2:1

Alvimopan
peripherally acting μ-opioid receptor antagonist accelerates GI recovery 12mg bd po
Ampakines
obtund opioid-induced side-effects

Tanezumab
humanised monoclonal antibody that sequesters NGF - effective analgesic in lumbar osteoarthritis

Opiorphin
inhibits breakdown of endogenous opioids (targets endocannabinoid system)

CB2 modulators
decreased intra-epidermal nerve fibre density after skin punch biopsy
I - New Delivery Systems

- Transdermal
to buccal, intra-articular intravesical routes

Transdermal drug delivery limited by stratum corneum

- Lipid-based nanocarriers
  (liposomes, lipid-core micelles, and lipid nanocapsules)

- Vesicular systems
  (ethosomes, transfersomes, and niosomes)

↓ toxicity of local anaesthetics and opioids

↓ toxicity of local anaesthetics and opioids

iontophoresis electroporation microporation phonophoresis
Liposome for Drug Delivery

- Lipid Soluble drug in bi-layer
- Lipid bi-layer
- Drug crystallized in aqueous fluid

(Lipton EA. Anesthesiol Res Pract 2012;2012:546409)
Magnetophoresis

(Shipton EA. TACC 2012: in press)
Iontophoresis

when current is applied drug cations are repelled; they move through skin, and absorbed into systemic circulation

(Shipton EA. TACC 2012: in press)
Fentanyl HCl PCTS is preprogrammed, needle free, self-contained drug-delivery system that uses electrotransport technology (iontophoresis) to deliver 40 µg of fentanyl per on-demand dose.

On-demand fentanyl HCl patient-controlled transdermal system (PCTS) - superior to placebo, well tolerated for the control of moderate to severe postoperative pain for up to 24 h after major surgery (Anesth Analg 2004;98:427-433)
Ethosomes

Lipid layer

Aq ethanolic sol of drug

(Shipton EA. TACC 2012: in press)
Spinal cord stimulation used for pain failed back surgery CRPS, angina, peripheral vascular disease

Neuro-Senza technology

Nevro-Senza technology

Peripheral nerve stimulation

Deep brain stimulation

Peripheral nerve stimulation neuropathic pain disorders, occipital neuralgia, migraine, subcutaneous leads

Deep brain stimulation technique for painful dystonia (CRPS); use in pain and cluster headache

Spinal cord stimulation used for pain failed back surgery CRPS, angina, peripheral vascular disease

Nevro-Senza technology high frequency signal, no paraesthesia

Deep brain stimulation technique for painful dystonia (CRPS); use in pain and cluster headache

Improved quality of life and function, many returning to work

Peripheral nerve stimulation neuropathic pain disorders, occipital neuralgia, migraine, subcutaneous leads

New perspective in cerebral ischaemia and vasospasm
Spinal Cord Stimulation
Successful Treatment of Testicular Pain With Peripheral Nerve Stimulation of the Cutaneous Branch of the Ilioinguinal and Genital Branch of the Genitofemoral Nerves

(Neuromodulation Jan 2012: in press)
<table>
<thead>
<tr>
<th>Types of surgery</th>
<th>Estimated incidence of chronic postoperative pain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy</td>
<td>15</td>
</tr>
<tr>
<td>Hip Surgery</td>
<td>10 – 20</td>
</tr>
<tr>
<td>Amputation</td>
<td>30 – 50</td>
</tr>
<tr>
<td>Breast surgery</td>
<td>20 – 30</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>30 – 40</td>
</tr>
<tr>
<td>Inguinal hernia repair</td>
<td>10</td>
</tr>
<tr>
<td>Coronary artery bypass</td>
<td>30 – 50</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>10</td>
</tr>
</tbody>
</table>
K - Perioperative Pain

Transition of acute postoperative pain to chronic post-surgical pain - complex and poorly understood

Involves altered pain processing

Intraoperative, postoperative surgical, psychosocial, socio-environmental patient-related factors

Multimodal analgesic drug combinations

Fast tracking multidisciplinary teams
### Risk Factors

Mark patients with high risk factors for developing persisting post surgical pain and follow up after discharge.

#### Preoperative

- Address patient attitudes and concerns
- Provide education (patient, physician)
- Identify operative procedures that cause severe pain

#### Intraoperative

- Use least painful surgical approach (e.g. keyhole) with acceptable exposure
- Use multimodal pharmacological analgesia in addition to afferent neural blockade

#### Postoperative

- Continue analgesia well into the postoperative period
- Measure pain levels (the ‘fifth vital sign’)
- Bedside neurological examination if neuropathic pain is suspected

#### Discharge

- Individualise discharge analgesic packages and home follow-up
- Use antidepressants (tricyclics) and anticonvulsants (gabapentin and pregabalin) as first-line co-analgesics if needed

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**Prevention and Management of Risk factors in Acute Perioperative pain for developing Chronic pain**

(Shipton EA. Anaesth Intensive Care. 2011 Sep;39(5):824-36)
Obtain patient preoperative information

Preoperative carbohydrate

No preoperative bowel clearance

Pharmacological ↓ stress

Optimise organ dysfunction

Avoidance of fluid excess-use of goal directed therapy

No routine use of drains

No routine use of nasogastric tubes

Early oral feeding

Early mobilisation

Objective pain assessment

Epidural analgesia or non-opioid multimodal analgesia

Discharge criteria

Daily care maps
Vertebraloplasty techniques for pain relief, stabilisation

Radiofrequency techniques (for tumour ablation, neurotomies)

Imaging Thoracoscopy give safer coeliac plexus and splanchnic nerve blocks

Intrathecal analgesia

Percutaneous cordotomy aided by computed tomography/MRI and endoscopy guidance

Percutaneous electrical nerve stimulation, 8% capsaicin patches used for neuropathic pain
Radiofrequency Machine
Percutaneous Vertebroplasty
M. Conclusion - Take Home Points

- Patterns of chronic pain in New Zealand are similar to international patterns
- Chronic pain represents a major health issue in New Zealand
- Optimal management of acute and chronic pain start with assessment of patients’ expectations, with weighing the pros and cons of potential drug therapies, and to determine an individualised treatment strategy
- Thorough patient assessment with regular review and pharmacovigilance ensure optimal efficacy and safety in prescribing
- Future therapies include focal therapy with sustained analgesic efficacy (capsaicin patches, botulinum toxin)
- Treatments acting on new targets, such as cytokine inhibitors, metabotropic glutamate inhibitors, and TRPV1 antagonists
- Early referral with acute persistent pain
Na\textsuperscript{+}, Ca\textsuperscript{2+}, and K\textsuperscript{+} Channels
Na$_v$1.9 following nerve injury

(a) *In situ* hybridization

(b) Immunocytochemistry

(c) Whole-cell patch-clamp studies

↓ in Na$_v$1.9 transcripts, protein and persistent TTX-resistant current in small neurons from dorsal root ganglia following axotomy
Rescue of *Scn11a* gene expression by glial-cell-derived neurotrophic factor (GDNF)

Addition of GDNF to cultures of dorsal root ganglia (DRG) maintained *in vitro* for seven days significantly upregulates (a) $\mathrm{Na}_v1.9$ transcripts, (b) protein and (c) persistent TTX-resistant current compared to control cultures. Scale bars, 25 m.

*(Trends in Neursciences 2004)*
C. Peripheral and Central Sensitisation
Neuroglial cells
Microspheres (or nanospheres) within a liposome

(Shipton EA. Anesthesiol Res Pract 2012;2012:546409)
A liposomal structure assembled from phospholipid molecules

(Shipton EA. TACC 2012: in press)
Neurostimulator

Extension

DBS lead

Shipton EA
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