COMMONWEALTH OF AUSTRALIA

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Pain – Update and Mechanisms

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Handout:

› SESSLE BJ. Recent insights into brainstem mechanisms underlying craniofacial pain. *Journal of Dental Education* 66; 108-112, 2002

On the web:

› Understand the complexity of the chronic pain experience
› Recognise chronic pain as a disease entity in its own right
› Understand muscle pain, using TMJ tenderness as an example (allodynia/hyperalgesia):
   - sensitisation of peripheral nociceptors
   - central sensitisation
› Comprehend referred pain, poor localisation of pain: pain source does not necessarily equal the pain site – important role of convergence and unmasking of latent connections
› Understand that the persistence of pain may lead to a permanent disease state through central sensitisation and neuroplasticity – importance of early intervention in acute pain
Introduction to pain: orofacial pain as an example

Peripheral mechanisms of nociception and pain
- Role of nociceptors in physiological pain, inflammatory pain and neuropathic pain (peripheral sensitisation)

Central mechanisms of nociception and pain
- Central sensitisation
- Referred Pain
How is Pain “officially” defined?

- Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage
  - Sensory experience: e.g. we can feel it, we know where it is
  - Emotional experience: e.g. we can feel worried or anxious or depressed

Definition from the International Association for the Study of Pain (IASP), the premiere organisation for the study of pain
Pain classification

- Acute pain
- Chronic pain
Acute Pain

- Acute or transient pain
- Evoked by a noxious stimulus
  - Noxious stimulus is a stimulus that is damaging or potentially damaging to the tissues
  - Eg thumb tack in a finger…OUCH!
- Useful biological function: it is protective
- Indicates that something is amiss
- Demands immediate attention and action
- Can usually be readily treated
Chronic Pain

› Pain lasting >3-6 mths
› No clear biological role
› Often associated with severe physical, social and/or emotional stresses for patient and family
› Staggering economic burden in Australia ($34 billion in 2007)*
› Largely unrecognized as a major health issue by health care policy makers
  - you cannot "see" chronic pain
› Chronic pain examples
  - Neuropathic pain
  - Temporomandibular disorders

*Access Economics P/L The high price of pain: the economic impact of persistent pain in Australia. 2007
Chronic pain is now regarded as a disease entity in its own right
- World Health Organization
- International Association for the Study of Pain

Recent evidence points towards chronic pain as being a neurological disorder in its own right
- that is, there is a disease of the nervous system (either peripheral or central) that is largely responsible for the pain

Sessle BJ *Journal of Orofacial Pain* 19; 5, 2005
Impact of Chronic Orofacial Pain

› Majority of orofacial pains: not life-threatening

› Major impact on an quality of life and economic productivity
  - prevent normal daily activities: work, social and recreational activities
  - pain behaviours, e.g., avoiding personal and social responsibilities, avoidance of self-management of pain
  - sleep problems
  - extensive health care use: drugs and doctors

› Temporomandibular disorders are similar to back pain (a major disabling disorder) in their intensity, persistence and psychological impact (von Korff et al. Pain 32; 173-183, 1988)

› THE PAIN MAY DICTATE A PATIENT’S LIFE

Nature Reviews Neuroscience 2005, front cover
Chronic Orofacial Pain

› Prevalence of orofacial pain ~12%
› Decrease in prevalence with increasing age
› Women report higher prevalence of orofacial pain than men
› People with orofacial pain had higher levels of anxiety and depression vs people without pain

Von Korff *et al.*, Pain 32; 173-183, 1988
What is Pain?

Pain is a complex sensation and has 3 main dimensions

- Sensory-discriminative dimension
- Motivational-affective dimension
- Cognitive-evaluative dimension
Pain is a multi-dimensional sensation

- **Sensory-discriminative aspects**
  - Location
  - Intensity
  - Duration
  - Quality
**Motivational-affective dimension:**

- conscious or unconscious drive state for a person to initiate, sustain or direct behaviour.
- related to the unpleasant feeling associated with pain, *e.g.*, feel unwell, depressed, *etc.*
- usually not associated with other sensations

University of Sydney gargoyle
Pain is a multi-dimensional sensation

Cognitive-evaluative dimension:

- pain is evaluated in terms of current and past experience
- interpreted in relation to the actual situation, e.g.
- footballer with broken limb and keeps playing unaware of the pain until that event finishes...then Ouch!
Nociception refers to the delivery and processing of signals in the brain following the activation of specialized sensory receptors called nociceptors or “pain receptors.” Activation of nociceptors does not necessarily lead to pain.
What is a nociceptor?

› Peripheral sense organ, or receptor, that responds to noxious stimulus
  - Noxious stimulus: a stimulus (e.g., chemical, thermal, mechanical) that can potentially produce tissue damage

› Widely distributed:
  - skin, mucosa, and deep tissues: muscles, joints

› Convert noxious stimulus to action potentials

› Nociceptors provide information about
  - Location, e.g. toothache can be localised to a quadrant
  - Intensity, e.g. VAS scale
  - Duration of a noxious stimulus to the body

› Sensory-discriminative aspects of pain

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Marchand et al., Nat. Revs Nsci. 6; 521-532, 2005
Activation of nociceptors in acute pain

- Acute mildly tissue-damaging stimuli (heat, cold, chemicals, e.g. capsaicin)
- Act directly on ion channels (e.g., TRPV1, transient receptor potential vanilloid 1) or
- Indirectly (via TRPV3, ATP), to generate action potentials
- Action potentials travel into brain

Marchand et al., Nat. Revs Nsci. 6; 521-532, 2005
Different types of pain defined according to the mechanisms

› Physiological or acute pain (e.g. pin prick)
  - Early warning device alerting us to the presence of damaging stimuli

› Inflammatory pain (e.g. ulcer)
  - Tissue damage

› Neuropathic pain (e.g. atypical odontalgia)
  - Pain that is caused by a primary lesion or dysfunction in the somatosensory nervous system

› Dysfunctional pain (e.g. some TMDs)
  - Disturbance in brain inhibitory control systems
Different types of pain defined according to the mechanisms

- Physiological or acute pain
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- Dysfunctional pain (e.g. some Temporo Mandibular Disorders)
  - Disturbance in brain inhibitory control systems
Inflammatory pain

Tissue damage recruits immune cells to the region

› Chemicals are released (e.g. interleukins, bradykinin)
› The chemicals sensitise the nociceptive terminal – called peripheral sensitization
› Now the nociceptor can respond to light touch or may even be spontaneously active and will send action potentials into the brain
› This can be interpreted as pain

Marchand et al., Nat. Revs Nsci. 6; 521-532, 2005
Peripheral sensitisation: sensitised nociceptors

- Spontaneous activity of nociceptors can result in spontaneous pain
- Lowered activation thresholds of nociceptors so that now these sensitized nociceptors respond to tactile stimuli. This results in allodynia, i.e. sensation of pain to a non-painful stimulus. Examples:
  - lightly touching sunburnt skin
  - pressing on tender muscles or tender TMJ in a TMD patient. Muscle strain from prolonged dental appointment can lead to chemical release and nociceptor sensitization

Peripheral sensitisation: sensitised nociceptors

- Increased responsiveness of nociceptors to a stimulus that is normally noxious. This results in hyperalgesia, i.e. enhanced sensation of pain to a painful stimulus.

- Everyday example: inserting a pin into sunburnt skin results in more pain than if there were no sunburn
Different types of pain defined according to the mechanisms

- **Physiological or acute pain**
  - Acute damaging stimuli

- **Inflammatory pain**
  - Tissue damage

- **Neuropathic pain**
  - Pain that is caused by a primary lesion or dysfunction in the somatosensory nervous system

- **Dysfunctional pain (e.g. some TMDs)**
  - Disturbance in brain inhibitory control systems
Nociceptors play a role in the following types of pain

› Physiological or acute pain
  - Acute damaging stimuli

› Inflammatory pain
  - Tissue damage

› Neuropathic pain
  - Pain that is caused by a primary lesion or dysfunction in the nervous system

› Dysfunctional pain (e.g. some TMDs)
  - Disturbance in brain inhibitory control systems
Summary: Peripheral mechanisms of nociception

› Nociceptors: peripheral sense organ
› Nociceptors play important role in
  - physiological pain
    - Chemicals activate ion channels to cause depolarisation and possible action potential generation
  - inflammatory pain
    - Chemicals activate ion channels directly and activate 2nd messenger cascades to cause sensitisation of nociceptors
  - neuropathic pain
    - Peripheral nerve lesions: spontaneous activity and changes in gene expression
  - dysfunctional pain
Nociceptive information enters brain stem

- Primary afferent cell bodies in trigeminal ganglion
- Fibres enter trigeminal spinal tract - part of trigeminal brainstem sensory nuclear complex
- Fibres terminate on neurones in subnucleus caudalis
What is Central Sensitization?

- Changes in the excitability of 2nd order (and higher) neurones in the Trigeminal Brainstem Sensory Nuclear Complex, e.g., change in Receptive Field properties and excitability
Windup of action potential discharge

- Slow excitatory post-synaptic potentials lasting tens of seconds
- 2nd order neurone: much more likely to fire action potentials and may fire spontaneously
- May lead to continuous pain
- Microglia also play a critical role in central sensitisation

Marchand et al., Nat. Revs Nsci. 6; 521-532, 2005
Central sensitisation

- May explain allodynia and hyperalgesia
- But also this central sensitisation may partly contribute to chronic pain if these central changes persist
- Possibility of a central disease state where periphery heals but central brain changes perpetuate the pain
- One of the reasons why chronic pain is regarded as a disease entity in its own right
- Recent evidence indicates that surgical incisions can lead to central sensitisation (Lam et al. Neuroscience 156 (2008) 737–747)
  - Indicates necessity for pre-emptive analgesia in general anaesthesia
  - If peripheral nociceptive input is blocked during the surgery and post-operatively, then this reduces central sensitisation and post-operative pain
Conclusions

› Understand the complexity of the chronic pain experience
› Recognise chronic pain as a disease entity in its own right
› Understand muscle/TMJ tenderness (allodynia/hyperalgesia):
   - sensitisation of peripheral nociceptors
   - central sensitisation
› Comprehend referred pain, poor localisation of pain: pain source does not necessarily equal the pain site – important role of convergence and unmasking of latent connections
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