WHAT HAVE THE PAST 40 YEARS OF RESEARCH INTO CRANIOFACIAL PAIN MECHANISMS TOLD US ABOUT CRANIOFACIAL PAIN STATES AND THEIR MANAGEMENT?

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Over the 40 years of his clinical and academic life, Steven Graff-Radford was committed to improving the diagnosis and treatment of craniofacial pain states. His many lectures and publications drew particular attention to the importance of research into pain mechanisms for the development of successful therapeutic approaches for headaches and other forms of craniofacial pain. This inaugural Steven Graff-Radford lecture highlights many of the research-based advances in our knowledge of craniofacial pain mechanisms over the past 40 years that have helped improve clinical understanding and management of craniofacial pain states.
OVERVIEW
Primary afferent mechanisms, including peripheral sensitization and modulatory processes.
Central nociceptive pathways and mechanisms, including central sensitization and modulatory processes.
The relevance of these mechanisms to the Diagnosis and Management of craniofacial pain states.

The Complexity and Multidimensionality of Pain

PRIMARY AFFERENT MECHANISMS
Peripheral Sensitization
OVERVIEW OF FINDINGS & CLINICAL SIGNIFICANCE

- Various chemical mediators influence the excitability of craniofacial nociceptive afferents and are involved in the pain-inducing effects of noxious stimulation and also in peripheral sensitization which may contribute to hyperalgesia, allodynia and pain spread.
- A sex difference exists in some nociceptive afferents' responses (e.g., to glutamate) that may contribute to sex differences in pain.
- Several therapeutic approaches exert their analgesic effects by targeting these processes, e.g., NSAIDs, LA patches, PHN vaccines.

Peripheral Sensitization

The peripheral sensitization of the peripheral nociceptive afferent endings is associated with their increased excitability and sensitivity to subsequent stimuli:

- Decreased activation threshold
- Increased responsiveness as well as
- Involvement of adjacent afferents which are implicated, respectively, in
  - Allodynia
  - Hyperalgesia
  - Pain spread

Example of peripheral sensitization, in a dural afferent
Craniofacial Nociceptive Pathways

- Primary afferents, with cell bodies in trigeminal ganglion
- Trigeminal brainstem sensory nuclear complex (and C1-2)
- Other brainstem areas, e.g. reticular formation (RF)
- Ventroposterior thalamus
- Other thalamic areas
- Cerebral cortex, e.g. somatosensory area, anterior cingulate gyrus

Most trigeminocervical nociceptive neurons have extensive convergent afferent inputs
Convergent excitatory facial and dural inputs to nociceptive trigeminocervical neurons

*Clinical Significance: Referred Pain/Allodynia*

Note analogies in coding of stimulus properties

Sex differences and sensitivity to light and hypothalamic modulation are also features of some trigeminocervical neurons

Light evokes neuronal responses that can be reduced by application to posterior hypothalamus of GABAα antagonist BMI

Modulation of neurons also evident in animal model of trigeminal autonomic cephalgias
Cortical spreading depression induced by cortical stimuli produces facilitation of trigeminocervical neuronal activity

From Price
From Hargreaves & Goodis, 2002

Trigeminal Subnucleus Caudalis (aka Medullary Dorsal Horn)

These findings in animal models have been complemented by correlated findings in human experimental pain models (eg, SEPs, MRI, QST)

Craniofacial nociceptive transmission is modulated by intrinsic CNS processes

Relevance of these modulatory mechanisms, or alterations in them, to clinical features of pain and its control

Stress/Anxiety/Depression
Analgesic Drugs
Cognitive Behavioural Therapy
Placebo Analgesia
Acupuncture-Induced Analgesia
DBS-Induced Analgesia
Disturbed Sleep
Sex Differences in Pain
Many of these modulatory mechanisms are inhibitory, but some may be associated with 'amplification' of pain. Neuroplasticity, and 'Central Sensitization'.

Trigeminal nociceptive neurons can undergo neuroplastic changes ('central sensitization') following acute injury or inflammation. Mustard oil to pulp induces NMDA-dependent central sensitization (eg, increase in receptive field size and responses of nociceptive neurons).

Central sensitization of nociceptive neurons is also evident at higher CNS levels of the trigeminal system (eg, thalamus, sensorimotor cortex), consistent with correlated findings in human experimental pain models.

Central sensitization can also be induced by dural stimulation.
Functional and structural changes also occur in CNS of patients with chronic craniofacial pain (HA, TMD, PTN).

Central Sensitization is reflected in neuroplastic changes in central nociceptive neurones, that is, the pain 'pathways' are not hard-wired but are 'plastic'. These changes have clinical correlates:

- Receptive field expansion (Pain spread and referral)
- Increased suprathreshold responsiveness (Hyperalgesia)
- Decreased activation threshold (Allodynia)

Although normally reversible, maintenance of these neuroplastic changes may set up a prolonged central hyperexcitable state leading to the development of a chronic pain state.
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These changes have clinical correlates:

- Although normally reversible, maintenance of these neuroplastic changes may set up a prolonged central hyperexcitable state leading to the development of a chronic pain state.

- Since central sensitization is induced by nociceptive afferent inputs, therapeutic approaches that reduce nociceptive inputs may decrease the likelihood of its development.

The involvement of several centrally acting chemical mediators, and glia, also provides therapeutic targets for the control of central sensitization and pain.

Central sensitization as well as peripheral sensitization may contribute to many craniofacial pain states (e.g. migraine) and both processes may be modulated by 5-HT-related drugs.

Early triptan treatment most effective in blocking development of trigeminal central sensitization.

From Goadsby et al, 2002.
Other drugs effective for pain relief in humans also suppress trigeminal central sensitization and associated pain behaviour. Trigeminal neuropathic pain model

Pregabalin attenuates nociceptive behaviour and trigeminal central sensitization following trigeminal nerve injury

Cao et al, J. Pain, 2013

These new findings support the clinical use of pregabalin in craniofacial neuropathic pain conditions.

Glia cells are important in trigeminal central sensitization occurring in acute or chronic craniofacial inflammatory or nerve injury states.

Chronic Pulpitis

GFAP

GS

FA blocks astrocyte Krebs cycle function, and SB203580 blocks p38 MAPK activity in microglia; both interfere with caudalis central sensitization.

Blockade of brainstem glial cell function overcomes trigeminal central sensitization

Chiang et al, 2007

Acute Pulpitis

Glial cell inhibition also blocks trigeminal central sensitization and nociceptive behaviour in chronic craniofacial pain models.
Findings in human studies (e.g. TMD OPPERA study of Maixner et al) have documented several genetic risk factors for clinical, psychological and sensory phenotypes related to pain onset.

Recent studies in animal models of craniofacial pain have shown that genetic factors (as well as environmental factors) influence expression of trigeminal central sensitization and associated pain behavior (Varathan, Cherkas & Sessle, 2013).

Some of these peripheral processes represent therapeutic targets for several current therapeutic approaches.

A better understanding of these peripheral processes is crucial for the development of new peripherally based approaches to control pain without CNS side effects.

SUMMARY

Many new insights into craniofacial pain mechanisms have resulted from clinical and experimental studies in animals as well as humans over the last 40 years, and have led to improved understanding of craniofacial pain and its control.

Various chemical mediators and receptor mechanisms have been shown to be involved in the peripheral processes of craniofacial pain. These include peripheral sensitization that may contribute to allodynia, hyperalgesia, and pain spread occurring in many craniofacial pain states.

Some of these peripheral processes represent therapeutic targets for several current therapeutic approaches.

A better understanding of these peripheral processes is crucial for the development of new peripherally based approaches to control pain without CNS side effects.

SUMMARY

The neurons and CNS pathways that signal acute craniofacial pain have been identified. They have properties that can explain many of the clinical features of craniofacial pain states and their modulation by “psychological” factors and several therapeutic approaches.

Neuroplastic changes reflected in central sensitization of these nociceptive neurons can result from peripheral injury or inflammation, and represent an important factor in several chronic craniofacial pain states and their management.

Trigeminal central sensitization is regulated by genetic factors, and this regulation may contribute to differences between individuals in the development and maintenance of chronic craniofacial pain states and in their response to specific treatment approaches.
SUMMARY

• Glia have been discovered to play a crucial role in pain states and may offer a novel therapeutic target for control of trigeminal central sensitization and other neuroplastic changes occurring in craniofacial pain states.
• The plastic capacity of both glia and neurons in the craniofacial nociceptive system represents a crucial target for the development of novel therapeutic approaches to manage craniofacial pain states.

In the insightful words of Steven Graff-Radford….

“the key to successful headache and pain therapy is research aimed at prevention and minimizing the plastic changes triggering chronic pain.”

Collaborators

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