

**REVIEW ARTICLE**

**NEUROPHYSIOLOGY OF PAIN : INSIGHT TO OROFACIAL PAIN**

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**Abstract :** This is a very exciting time in the field of pain research. Major advances are made at every level of analysis from development to neural plasticity in the adult and from the transduction of a noxious stimulus in a primary afferent neuron to the impact of this stimulus on cortical circuitry. The molecular identity of nociceptors, their stimulus transduction processes and the ion channels involved in the generation, modulation and propagation of action potentials along the axons in which these nociceptors are present are being vigorously perused. Similarly tremendous progress has occurred in the identification of the receptors, transmitters, second messenger systems, transcription factors, and signaling molecules underlying the neural plasticity observed in the spinal cord and brainstem after tissue or nerve injury. With recent insight into the pharmacology of different neural circuits, the importance of descending modulatory systems in the response of the nervous system to persistent pain after injury is being reevaluated. Finally, imaging studies revealed that information about tissue damage is distributed at multiple forebrain sites involved in attentional, motivational, and cognitive aspects of the pain experience.

**Key words :** pain pathways evaluation pain relief  
orofacial pain evoked potentials TSEPs

**INTRODUCTION**

**Pain : the International perspective**

A Committee of the International

Association for the study of pain has defined pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (1). It is mostly accompanied by the desire to stop and to avoid stimuli

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causing it. It is linked with a feeling of aversion (2). Throughout most of recorded history, pain was characterised as an effective feeling state rather than a sensation (3). Emotions play a key role in painful experience. Aristotle described pain as a "passion of soul", distinct from the classic five senses (4).

Melzack and Wall (5) and Melzack and Casey (6) developed a model of pain in which tissue damage concurrently activates sensory, discriminative, cognitive-evaluative and affective-motivational components of pain.

### Substrates of pain: neuroanatomy of pain pathways

#### *Receptors of pain*

Sensory receptors for pain, nociceptors, are naked nerve endings that terminate in the skin and most other tissues of the body. However, their distribution is not uniform throughout organs of the body. As a general rule, deep visceral organs of the body are not well supplied with nociceptors. These receptors are generally classified according to the type to which they respond:

1. Mechanosensitive pain receptors respond to mechanical damage.
2. Thermosensitive pain receptors respond to respond to temperature extremes.
3. Chemosensitive pain receptors respond to chemicals that occur with damaged tissues example hypertonic saline, potassium chloride, acetylcholine, 5-Hydroxytryptamine, histamine, bradykinin and substance P. Vasoactive amines are released just after injury by the basophils, platelets and mast cells.

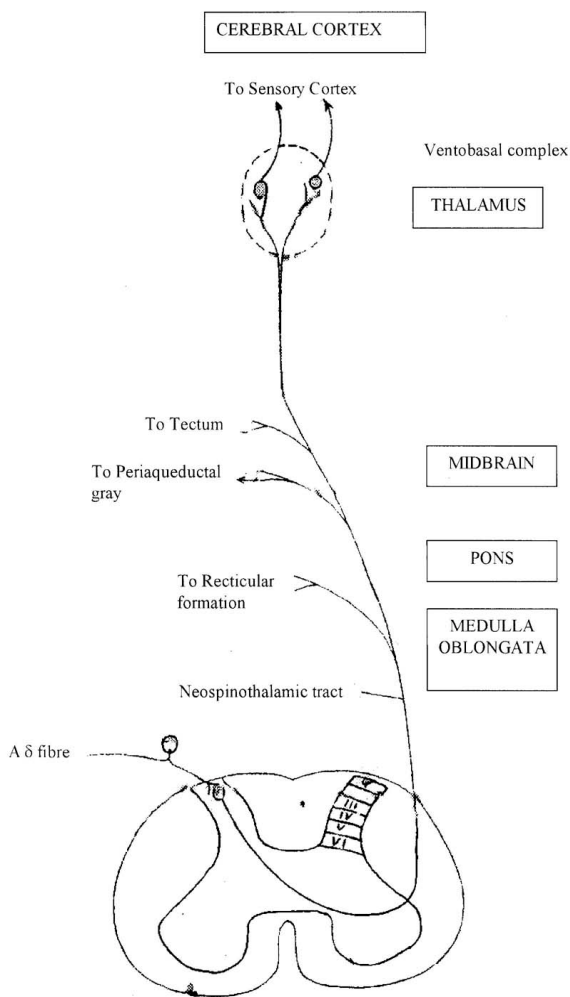
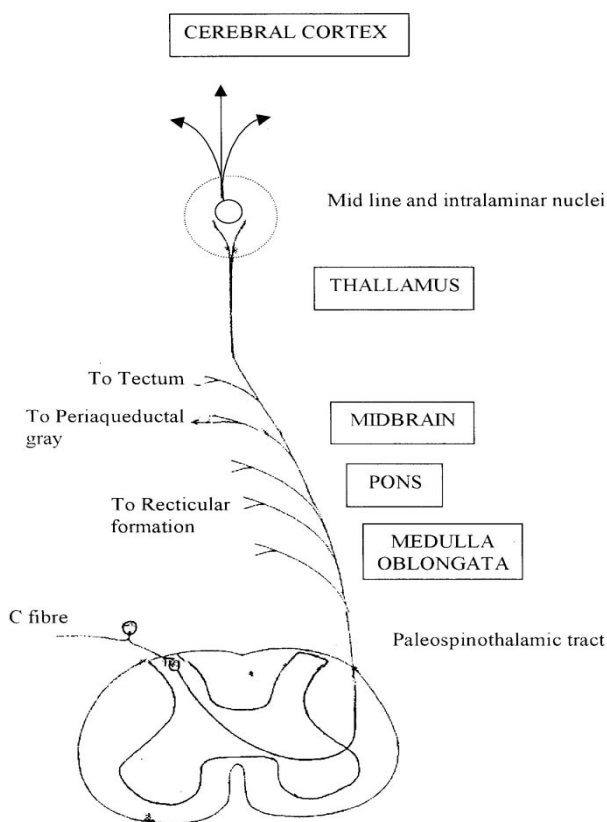


Fig. 1: Pathway by which Fast Pain is conveyed to the Central Nervous.  
I-VI: Laminae of the Dorsal Horn of the Spinal Cord.

As these receptors signal either actual or potential damage to tissues, pain has survival value to the organism. Consequently pain receptors generally do not adapt to



Pathway by which Slow Pain is Conveyed to the Central Nervous System

Fig. 2: Pathway by which slow pain is conveyed to the Central Nervous System.

prolonged stimulation. In fact pain sensation may intensify as pain thresholds become lowered through continued stimulation (7).

From the peripheral receptor to the cerebral cortex, specialised neural pathways termed the nociceptive system process noxious stimuli. Peripherally, noxious stimuli activate specific receptors (nociceptors) of thinly myelinated A $\delta$  and unmyelinated C fibers terminating in the spinal cord dorsal horn. Neurophysiological

evidence for the existence of cutaneous myelinated A $\delta$  and unmyelinated C fibers was provided by Zottermann (8-10), who interpreted his observations as strong support for Bell's and Mullers theory of specificity (11,12). It is known that noxious stimulation exciting somatic and dental A $\delta$  afferents may exert a masking or inhibitory effect on C-fiber related sensations. Tables I to III describe the peripheral mechanism and recent developments in ion channels, neural transmission and transduction for pain sensation.

#### Molecules involved in pain transmission

The role of trophic factors and cytokines in the development and maintenance of pain in response to various forms of tissue injury is an area of research that has virtually exploded in the last several years.

In addition to its role in development, NGF and other growth factors, and cytokines have been shown to mediate pain and hyperalgesia associated with tissue injury.

Lorne Mendell (20) the first to describe the link between NGF mechanisms underlying the initial hyperalgesic response to NGF. The initial hyperalgesia in response to systemic or peripherally administered NGF depends on indirect mechanisms, specifically mast cell degranulation.

Linda Watkins (21) described additional pathways through which activation of the immune system results in changes in multiple sites throughout the nervous system. Watkins described the molecules involved in the signaling pathways as well

TABLE I: Characteristics of fast and slow fibers (7).

<i>Fast (Diagram 1)</i>	<i>Slow (Diagram 2)</i>
Carried by A $\delta$	By C fibers
Sharp, pricking sensation	Dull, aching, burning
Easily localised	Poorly localised
Occurs first	Occurs second; persist for longer time, more unpleasant
Occurs on stimulation of mechanical and thermal receptors	Occurs on stimulation of polymodal receptors

TABLE II: Recent developments on Ion channels &amp; nociception in the peripheral nerve.

<i>S.No.</i>	<i>Scientist/Researcher</i>	<i>Work</i>
1.	Steve Waxman (13)	Indicated Dynamic changes of expression of TTX-sensitive sodium channel contributing to hyperexcitable nociceptors after injury
2.	Michael Gold (14)	Role of Modulation of TTX-resistant sodium currents by PGE <sub>2</sub> , 5HT, and adenosine modifies mechanical induced hyperalgesia during inflammation.
3.	Daniel Weinrech (15)	Role of Ca <sup>++</sup> dependent K <sup>+</sup> current in controlling excitability of vagal afferents.
4.	Peter McNaughton (16)	Presented evidence implicating activation of Protein Kinase heat activated channel by bradykinin

Note: These mechanisms explain the ionic basis of increase in hyperexcitability in presence of nociception.

TABLE III: Transduction transmission and modulation of nociceptive information.

<i>S.No.</i>	<i>Scientist/Researcher</i>	<i>Work</i>
1.	Amy Mac Dermott (17)	Experiments on the role of presynaptic non-NMDA & kainate receptors in dorsal root ganglion neurons. Activation of these receptors appears to influence glutamate release from the sensory neuron & therefore activation of dorsal horn neurons.
2.	Edwin McCleskey (17)	Using Electrophysiology, single-cell PCR and reverse transcription PCR reactions determined the number of mRNA copies encoding the $\mu$ -opioid receptor in a single cell. Their results explained perplexing aspects of opioid analgesia.
3.	Michael Salter (18)	Provided evidence-supporting development of long-term potentiation in the hippocampus and by analogy, central sensitisation of spinal cord dorsal horn neurons after tissue injury.
4.	Edward Perl (19)	Pointed changes in $\alpha$ -adrenergic receptors present in sensory neurons after injury. Expression of the receptors involved in transmission of nociceptive stimuli contributes pathophysiology of pain.

Note: Researchers on receptors involving the transduction, transmission, and modulation of nociceptive information is clearly one of the most exciting and rapidly advancing involved in the transmission of nociceptive stimuli as well as the cellular elements necessary for synaptic transmission. Researchers have begun to collect together the essential elements for the first steps ultimately leading to the perception of pain.

as how activation of this system results in changes in behavior.

Steve McMohan (22) summarised the growing body of data implicating a critical role for brain derived neurotrophic factor in the altered nociceptive processing observed in the presence of inflammation.

Brain derived neurotrophic factor appears to function as a neurotransmitter/Neuromodulator in the dorsal horn of the spinal cord, where it is released from the central terminals of small-caliber afferents and increases the excitability of dorsal horn neurons.

#### **Spinal integrating mechanism of pain**

From the pain receptors, pain impulses are carried to the CNS by two fiber systems: the large myelinated fibres (A-delta) conduct impulses rapidly (15.25 m/sec), the small unmyelinated fibres (C-fibres) conduct at a slower rate (<1 m/sec). Both types of fibres occur in peripheral nerves and connect pain receptors to the spinal cord. Within the cord, these fibres synapse in the dorsal gray matter and the substantial gelatinosa (SG). The SG cells are thought to serve as an integration centre and relay system for pain sensations, although their exact role in pain process is not known. However, this area of spinal cord has many interconnections with other gray matter neurons and it has a large number of opiate receptors and an abundance of substance P. Substance P is a neurotransmitter that is apparently unique to pain fibers of spinal cord. Cells of the cordal gray matter send axons across the midline to ascend in the lateral

spinothalamic fibres synapse with relay neurons of the thalamus, which project upwards to the postcentral gyrus of the cortex to complete pain pathways.

Besides, spinal integrating mechanism, diencephalic and brainstem, analgesic-descending influences impinge upon SG to integrate pain sensation at the cord level.

#### **Gate-control theory for pain relief**

This theory proposes a physiological basis for reduction of perceived pain by gentle tactile stimulation over the affected site (e.g. abdominal pain is subjectively reduced by lightly stroking the skin over the abdomen). A network of "t-cells" (cells propagating pain from slow fibres) and interneurons that can inhibit the t-cells is postulated to form a gate within the dorsal horn spinal cord. The faster propagated fibres that carry information about light touch, thus inhibiting "t-cells" and decreasing the transmission of pain impulse actuate the interneurons. Although the exact site of gate network is not known the principles of the theory have been accepted and applied clinically. Tactile stimulation that is used to "close the gate" can be replaced by electrical stimulation of the pathways of light touch through electrodes placed on the skin, as is done in Transcutaneous electrical nerve stimulation TENS or electroacupuncture.

#### **Natural endogenous algesic and analgesic mechanism (Fig. 3)**

Opium was determined to be "God's own medicine" for pain. Not only does opium produce definite analgesic effects, but it also

eliminated fear, anxiety and suffering. The opiate receptors are part of the naturally occurring or endogenous, analgesic mechanism within the human nervous system. Analgesics relieve pain and the most potent analgesic is the morphine. It complexes with opiate receptors associated with synaptic terminals of the substantia gelatinosa and the gray matter that surrounds the third ventricle of the brain stem (periaqueductal gray). Morphine when complexed with opiate receptors, reduces or eliminates pain.

With discovery of opiate receptors, came a search for their natural function.

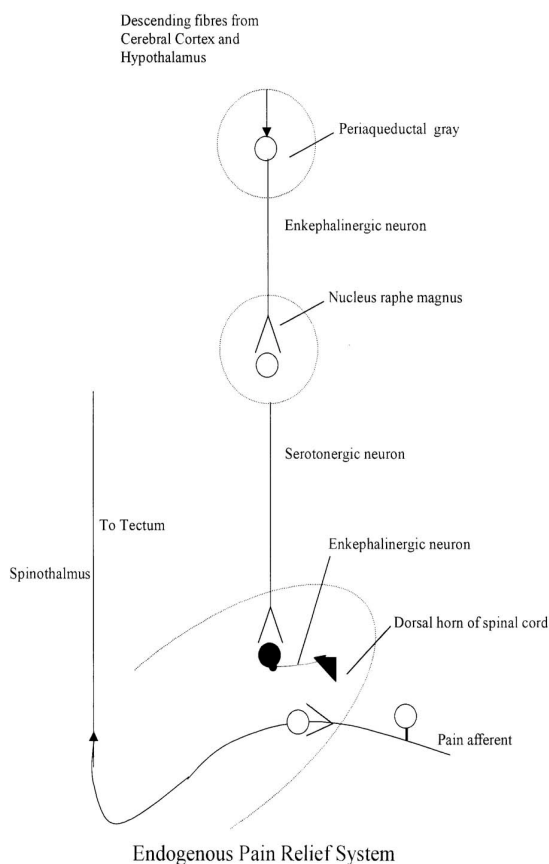


Fig. 3: Endogenous Pain Relief System.

Consequently, naturally occurring (Endogenous) opiate compounds were found. These compounds are collectively called as Endorphins. Three-endorphin compounds-met (methionine) enkephaline, leu (leucine) enkephalin and beta endorphins are known to play a role in natural pain suppressing mechanisms. These are produced at different levels of CNS as a result of painful stimulation. They serve to raise pain threshold and reduce pain.

### Phantom limb and plasticity

Amputation of limb is often followed by the feeling that limb is still present. This phenomenon is termed as phantom limb and enhances our understanding of pain pathways. The phantom area gradually shrinks and may completely disappear. But in 5 to 10% amputees; there is a persistent and severe pain apparently from the absent region. The pain is thought to be of central origin. On sectioning of contralateral spinothalamic tracts pain may be relieved for long periods by a prolonged or severe stimulus to the stump; although in others the stump may be reamputated or anaesthetised without any relief.

“Fooling the brain” may relieve pain. A mirror is applied in between the amputated limb and the normal limb. The patient is asked to look in the mirror and move his normal limb. Visual stimuli of movement of normal limb make the individual feel as if his amputated limb is moving. This brings back a surge of plasticity changes in the cortex, which are linked to surge of emotional changes that relieve the limb from its “locked” position at the time of amputation (7).

Marie Fitzgerald (23) reported changes in the neonatal spinal cord that are incomplete versions of what occurs in the adult. Central sensitisation occurs in the response to electrical stimulation of A  $\beta$  fibers whereas activity – induced plasticity in the adult spinal cord takes place only in response to C fiber strength stimulating unless the dorsal horn is primed by previous peripheral injury. NMDA receptors are distributed in higher density in the neonatal cord.

Clifford Woolf (24) provided an outstanding, concise and up to date review of activity-induced and signal induced plasticity in sensory neurons after tissue injury.

#### **Referred pain: Its significance**

The pain originating from viscera is generally of slow, aching type, which is difficult to localise. Frequently visceral pain may be referred to other parts of the body supplied by the same spinal nerve (the dermatomal rule) known as referred pain. When pain is referred to another part of the body, the site of referral is usually a part of the body that develops from the same embryological segment or dermatome, as the affected source of the pain. The same peripheral nerves supply these common regions of the body. For example, the heart and arm are derived from the same dermatome, and the kidney, ureter and testes are all derived from another common dermatome.

Clinical significance of classical referred pain lies in diagnosis. Usually visceral pain of the abdomen may cause overlying, abdominal muscles to contract. This

increased rigidity “guarding” helps in localising the possible source of pain in particular viscera. Gall bladder pain is referred to right shoulder tip and cardiac pain to left shoulder and upper arm. Such referred pain thus helps in making correct diagnosis of the diseased viscera.

#### **Subcortical mechanisms**

##### *Pituitary mechanisms*

Melzack R. postulated the existence of a pain neuromatrix in which the experience of pain is produced by multiple influences and comprises of a widely distributed neural network with input from the body’s stress-regulation systems, including Hypothalamic Pituitary axis (HPA) and opioid systems. Facial pain itself may act, on the other hand as a strong activator of the HPA. (25)

#### **Cerebral cortical mechanisms**

The current knowledge of pain perception is quite fragmentary. The role played by the cerebral cortex in pain is not clearly understood. If the post central gyrus (somatosensory area) is electrically stimulated, very few patients report a sensation of pain. The cortex is thought to aid in the appreciation of pain, but the responses to painful stimuli persist even when the cortex is surgically removed. A great deal of evidence implicates the thalamus in the perception of pain.

#### **Newer concepts of understanding cortical mechanisms**

A considerable amount of evidence suggest that Primary Somatosensory cortex

(SI) has a pivotal role in sensory discriminative aspects of pain such as spatial discrimination (26) and intensity coding (27).

Cognitive factors can alter the perceived intensity of pain and accordingly, can modulate SI activity in functional imaging studies. Physiologically, inhibition of nociceptive neurons and neurons with non sensory discriminative response characteristics may be involved in this cognitive modulation and in interaction of pain and touch in SI area.

Neurophysiologic and functional imaging data clearly indicate participation of SII in human pain processing. Preserved, direct thalamic access of nociceptive information to SII, supported by anatomic thalamocortical connections and by parallel activation of somatosensory cortices, suggests a particular relevance of this area in pain processing.

Functionally, SII may be involved in recognition, learning and memory of painful events (26,28-32)

Numerous functional imaging studies indicate participation of anterior insular cortex in human pain processing. Recent findings indicate a dedicated pain and temperature pathway to the insula need to be integrated with functional imaging data. Functionally the insula may be involved in automatic reactions to noxious stimuli and in pain-related memory and learning (33-35).

Clinical reports that patients with cingulotomies sometimes still feel pain but report it as less distressing along with findings that high level of opioid binding

occurs in the Anterior cingulate cortex (ACC). Pain affect (i.e. unpleasantness of pain) is encoded in the ACC.

By using hypnosis, Rainville et al (36) selectively altered unpleasantness of noxious thermal stimuli without changing the perceived pain intensity.

Analysis of cerebral activation pattern as measured by PET revealed that the modulation of pain affect was paralleled by activation changes in the ACC but not in the other brain tissues.

Along with these and other studies the proximity of the nociceptive, motor and cognitive regions of the ACC suggests possible local interconnections that may allow the output of the ACC pain area to command immediate behavioral reactions (37-40)

### **Grading/Evaluation of pain**

Pain is a complex physiological-behavioral puzzle that requires assessment on different levels.

At the same time the measures of pain should be reliable and valid, other wise they will be of little use to clinicians or researchers (41). An ideal pain measure (42) should provide sensitive measurement free of bias, provide immediate information about accuracy and reliability. The measurement should also separate the sensory-discriminative aspects of pain from its hedonic qualities assess experimental and clinical pain with the same scale and provide absolute scales that allow assessment of pain between groups and within groups over time.



The pain threshold can be determined by the classical methods. Simple category scales such as four-point “none, mild, moderate and severe” (verbal categorical scale) or 1-10 numerical scale can be scored in several ways. The simplest, the method of equal appearing intervals assigns successive integers to verbal categories directly (43). The three most frequently considered aspects of pain are the subjective (Measured by self-report), the behavioral (measured by sampling of physiological or electric potentials and assaying body fluids or other biological responses.) Self-report measures, when they can be obtained, should be regarded as the “Gold standard”. Indeed, the International Association for the study of pain emphasises that pain is always subjective.

Fortunately, techniques for the psychological assessment of the pain patients have improved to the extent that emotional stress such as anxiety, depression and defensive personality styles can now be identified. People experiencing pain are able to report separately on the sensory and affective dimensions and emotional qualities differ dramatically across different forms of clinical pain and within individuals over time (44). Currently evidence indicates that pharmaceutical and psychological interventions have different effects on either sensory, affective or both qualities of the experience.

### **Subjective pain assessment**

A Visual Analogue Scale (VAS) is a simple measure of subjective pain. It consists of a 10-cm horizontal or vertical line with two end points labeled “no pain” and “worst pain ever”.

The subject is required to place a mark on the 10-cm line at a point, which corresponds to the level of pain intensity the subject presently feels. The distance in cm from the lower end of the VAS to the patients mark is used as a numerical index of the severity of pain. (45,46)

The VAS is sensitive to pharmacological and non-pharmacological procedures that alter the experience of pain (47) and correlates highly with pain measured on verbal and numerical rating scales (48,49). The ease of administration and scoring has contributed to the popularity of this method. A major advantage of the VAS as a measure of sensory pain intensity is its ratio scale properties (50), minimal intrusiveness and conceptual simplicity (51).

The traditional view that the cerebral cortex is not involved in pain processing has been abandoned during the past decade based on anatomic and physiologic studies, lesional studies, functional neuroimaging and neurophysiologic studies in humans.

The use of techniques such as micro-recordings of the unitary or multiunitary activity of the nerves or nuclei, intracranial evoked potentials, nociceptive evoked potentials, reflexology, polysomnography and topography together with techniques such as percutaneous objective localisation of deep nerves, allows quantitative evaluation pre-intra and postoperatively (52).

### **Evoked Potentials**

Specific stimulation at periphery causes nerve impulses to be conveyed to the brain sensory areas producing at the cerebral

cortex an electrical potential change called the Cortical Evoked Response. This potential change cannot be recorded as a single response because it is too small to show up against the normal variability of the electroencephalogram (EEG). However, if a considerable number (say 50 or more) of evoked responses are produced and the EEG tracings are analysed by a suitable computer, the average response becomes apparent after due amplification.

Evoked potentials are a complex summation of graded potentials along afferent pathways and at the cortex by peripheral volleys. (53)

It is tempting to regard this evoked potential response as an indicator that the neural impulses initiated by the stimulus have reached consciousness, and that it is a physical indicator of perception, but two factors are not necessarily coincident. (54)

### **Pain and cognition**

Event Related Potentials (ERP) are valuable and useful parameters for assessing a variety of cognitive abilities (55) and psychological processes including expectancy, attention, search, discrimination, decision – making and memory. P 300 is a valuable tool and our preliminary work have shown that it can evaluate the cognitive and affective components of pain (56-59)

A significant increase in P 300 latency in patents suffering from pain as compared to age and sex matched controls. Our finding suggest that there are cognitive changes in chronic pain states. This cognitive blunting

is reversible with analgesic intervention. (60). Contingent Negative Variation (CNV) is a surface –negative slow potential recorded from human subjects during a fixed foreperiod of a warned reaction time task. (61).

The electrical phenomenon of the brain, has drawn the interest of many psychophysicologists because it reflects some psychological processes such as expectancy, motivate attention and arousal. The CNV waveform depends primarily on psychological and to a lesser extent on physical proportion of the stimulus.

CNV can be used to evaluate the affective-emotional components of pain. It is still unclear how brain processes emotionality and pain, and what are the interaction mechanisms of emotion and pain.

Slow brain potentials in the contingent negative variation (CNV) are found to be larger in the pain condition than that of the control (62-64). When patients with chronic pain were studied in The CNV paradigm, the appearance of CNV response was more marked. It was concluded that slow evoked potentials are sensitive to anxiety level and to pain perception. Rizzo (65) have shown the usefulness of this measure in the investigation of pain as a complex sensation. A number of recent studies have assessed the influence of baseline or induced mood on subjective and psychological responses to experimental stimulation. Baseline (66) and induced (67) anxiety have been shown to increase pain ratings to thermal or pressure pain ratings, while an experimentally induced depressive mood (induced by

presentation of text with depressive themes) decreased tolerance to cold pressor pain (68). Pain memory processes have been investigated using experimental painful stimulation (69). These studies provide experimental examples of how the experience of chronic pain can exert subtle influence on cognitive processes and mood. Pain itself can also impair cognitive and psychomotor performance.

### **Pain evoked potentials**

Evoked Potentials (EPs) are stimulus or event related electrical signals of brain activity that may be recorded from the scalp when precisely controlled discrete stimuli are delivered.

Significant correlation exists between late EP components by experimental pain stimuli and the induced pain sensation.

EPs can serve as indicators of perception at multiple levels. Pain related brain evoked potentials are recognised as an objective and quantitative test for evaluation of peripheral and central spinothalamic tract, thalamocortical projections and cortico-cortical circuit for pain processing.

Chen et al (70) identified the current source dipoles in noxious information processing.

The pain related components late and ultra late are distributed bilaterally in both hemispheres exhibit maximum amplitude in the vertex. The late components are assumed to reflect secondary mechanisms of information processing, such as stimulus recognition, localisation, estimation of

stimulus intensity and painfulness and initiation of motor movements.

Further analysis by Chen et al (70) on the consistency and reliability of the pain-related sources revealed that two pain related components are consistently found a negativity at 145 msec. and a positivity at 225 msec. The initial components correlate with stimulus intensity and appear to code information about intensity of the external stimulation. The latter components are closely related to the subjective estimation of pain intensity and seem to reflect association processes involved in evaluation of noxious stimulus.

Chen et al findings suggest that the late components of the EP waveform may reflect the cognitive aspects of dental pain perception in laboratory models.

When analgesic interventions are introduced subjective reports of pain intensity is reduced and EP components diminish accordingly.

Zelansky et al (71) suggested that the pain-EP reflects the emotional-motivational response to pain rather than the sensory-discriminative components.

### **Somatosensory evoked potentials**

Following stimulation of sensory receptors, a series of electrical events ensues in the afferent pathway and in the brain, and this activity may be measured non-invasively from sites on the body surface. The waveform is known as Somatosensory Evoked Potential.

The evaluation of somatosensory evoked potentials is mainly related to assessment of a particular nerve to central nervous system pathway.

Results in our studies have demonstrated that there is a change in the absolute peak latency of N19 in patients with chronic pain.

### **Imaging: MRI and SPECT**

During the last decade, advances in functional brain imaging techniques have led to identification of neuroanatomic substrates of pain perception. Human lesion studies using computer tomography and MRI, and functional neuroimaging studies using Single-Photon Emission Computed Tomography (SPECT), positron emission tomography (PET) and functionally (fMRI).

Ken Casey (72) described the role of for brain mechanisms of pain in imaging in humans and reviewed convincing evidence that the perceived intensity of unilateral pain evoked by different input as correlates with increases in regional cerebral blood flow in primarily five structures. Bilaterally in the thalamus, the contralateral insula, the bilateral premotor cortex, the contralateral anterior cingulate and cerebral vermis.

The combined use of psychosocial dimension and imaging in humans should help reveal the functional role of different forebrain structures that have direct corticofugal projections to the thalamus, brain stem, and spinal cord, and thereby modulate the pain experience at those levels.

These studies non-invasively demonstrated involvement of distributed cerebral areas in

human pain processing involves a variety of subcortical and cortical regions. More recently, topographic aspects of pain representations in the cerebral cortex have been extended to the temporal domain by results of neurophysiologic studies using whole scalp magnetoencephalography (MEG) and EEG (73).

Thus it may be concluded that pain is a personal, subjective experience influenced by cultural learning, the meaning of the situation, attention and other psychological variables. Approaches to measurement of pain include verbal and numeric self-rating scales, behavioral observation scales and physiological responses. The complex nature of the experience of pain suggests that measurements from these domains may not always show high concordance. Further development and refinement of pain measurement techniques will be able to meet the challenge and lead to increasingly accurate tools with greater predictive powers.

### **Orofacial and dental pain**

#### *Introduction to dental pain*

Face is considered as a mirror of mind. Inward events, emotions, behaviors are reflected on facial expressions. The cortex is also a mirror image to the body. It reflects the body image and perceives what the body experiences. The cortical homunculus of the body has wider representation for orofacial area as compared to other parts. This is elucidated below in detail along with the clinical significance.

When a patient comes to the dentist and complains of pain, the dentist is not dealing

with a simple sensory phenomenon involving the peripheral neural events elicited by painful stimuli. Pain in dentistry has a sensory –discriminative dimension. It provides information about the noxious stimuli-characterised by quality, intensity, location and duration, pain from other regions may not reflect that, where

Pain has multidimensional emphasis, involves affective, motivational and cognitive components. In orofacial pain for example the patient's last visit to the dentist, and ongoing sensory experiences of stress and anxiety during the current visit may modulate the pain experience. (73,74).

Sensory disturbances of the face and oral cavity can occur in number of situations that are of particular interest to the oral and maxillofacial surgeon. These include nerve lesions during removal of mandibular cysts, third molars, osteotomies of the facial skeleton and maxillofacial trauma.

Temporo Mandibular Disorders (TMD) comprise by far the most common cause of chronic facial pain conditions with a higher prevalence in women as compared to men (75). TMD are a complex heterogeneous group of conditions, involving masticatory muscles and/ or temporomandibular joints, characterised by chronic facial pain and representing cause of physical and psychological debility in a large segment of population.

#### **Accompaniments of pain**

##### *Sensory-discriminative system (76)*

Under ordinary conditions, a noxious stimulus can quickly be localised in time and

place. Somatosensory and dorsolateral spinal cord are so organised that this spatiotemporal information is rapidly transmitted. The dorsal column nucleus is topographically organised so that cells responding to stimulation from a small area of the body are clustered together and are physically adjacent to the neurons that receive input from contiguous areas of the body. This system allows identification of pain duration and its exact location.

A secondary input into the posterolateral and ventral posterolateral thalamic nuclei is from direct spinothalamic tract input by means of fibres that ascend in the ventrolateral spinal cord-the classic pain pathway. These rapidly conducting neurons form an alternate pathway for discriminative somatosensory functions.

##### **Motivational-affective system (76)**

The paleo spinothalamic system consists of fibers of the ventrolateral system that synapse in the reticular formation of the brain stem, where neurons form a complex network with extensive connections to ascending and descending systems.

This complex system may provide the neural pathways for the aversive-motivational component of pain-the suffering aspects often associated with painful experiences. In addition to interactions with the limbic system and the hypothalamus, the system projects to periaqueductal gray matter, where it interacts with descending impulses that ultimately aid in the modulation of impulse transmission within the spinal cord.

Many drugs, particularly narcotic analgesics, can alter the aversive-motivational aspects of the pain experience. That is, these agents reduce fear and anxiety and can eliminate the suffering aspects associated with pain. Indifference to noxious stimulus is brought about in this manner. Patients may state that the pain has not decreased in intensity but they are no longer bothered by it. Drugs create this indifference to pain.

#### **Activation of motor mechanisms (76)**

Motor mechanisms that are responsible for many of the overt reactions to pain are interrelated with spatio-temporal analysis and affective aspects of the experience of pain. Once integrated within the central nervous system, the impulse triggers a sequence of responses characterised in the individual by:

- 1) Startle response
- 2) Flexion response
- 3) Postural readjustment
- 4) Vocalisation
- 5) Orientation of the head and eyes to examine the damaged area,
- 6) Evocation of past experience in similar situations,
- 7) Prediction of the consequence of the stimulation, and
- 8) Many other patterns of behavior aimed at diminishing the sensory and affective components of the entire experience.

Facial grimacing, clenching the teeth, crying and other manifestations of the

experience may occur. Change in vital signs may also occur. Sympathetic nervous system function is generally enhanced as well.

Thus the pain center, as postulated by the specificity theory, has been replaced by the encompassing global concept of an action system. The system is not only responsible for identification, appreciation, recognition, and reaction to the unpleasantness impulses arriving from the periphery, but it is also intimately involved with the modulation of impulse transmission at spinal cord (or trigeminal nucleus) levels.

#### **How different is this pain from general pain? : peculiarities of dental pain**

The tooth pulp has many attractive features for the study of peripheral pain mechanisms because of its rich innervation, its unique distribution of nerve fibers and its general disposition to give rise to pain upon stimulation (76-84). In the last century, three theories explaining the exact mechanism of sensitivity of dentin, this seemingly inert structure has been elucidated:

1. Pain is a direct result of stimulation of sensory nerve endings in the dentin. The most sensitive area of the tissue is near the dentoenamel junction.
2. Odontoblasts are sensory cells. They receive and transfer stimuli to nerve endings in the pulp.
3. Hydrodynamic theory: Dental sensitivity is a result of mechanical stimulation of free endings in the pulp caused by rapid

fluid flow in the dental tubules where the dentin is stimulated.

Orofacial pain can be as severe as any pain experienced and includes cases of intractable pain as well as acute pain. Moreover personal, family and social cost of this is enormous, not just in terms of financial loss and cost of treatment but also in the risk of drug addiction, multiple operations and even suicide. These features are peculiar to orofacial pain. The most frequent source of orofacial pain is dental disorders and it has been estimated that toothache is suffered for upto five million days, and one million nights sleep lost as a result of it, in one year, in Britain alone (85). This article helps the reader develop his understanding of orofacial pain in particular, with an object of exploring the newer techniques and procedures that improve his diagnostic ability for better treatment.

### **Psychology of dental pain**

Perhaps the most important factor affecting reaction to pain is basic emotion of fear. A pain in the leg might well elicit less of a reaction than a pain of equal intensity in the chest because the latter might appear to the sufferer to signify heart disease. Pain in the head (including the face) are also regarded with greater apprehension since they might appear to threaten the innermost being including mind and thought processing in the cortex. Pain distorts this normal inner image causing a feeling of revulsion. The clinician attempts to see this picture to determine its attributes, characteristics. This article in further is a step in this direction analysing newer methods of electrophysiology

to understand this "blurred" image in order to improve the diagnostic ability and treatment.

### **Pathways of orofacial pain: neuroanatomy (Diagram 4)**

Sensory input from peripheral receptors is carried along the trigeminal pathway to the somatic sensory areas of the cerebral cortex via a 3-neurone chain. The cell bodies from the Trigeminal (Gasserian) Ganglion and this main nerve bundle then enter the brainstem at the level of the pons. These fibers synapse for the first time at the main sensory nucleus of the V<sup>th</sup> nerve (discriminative tactile senses, light touch and pressure) or alternatively at descending spinal tract nuclei, the N. caudalis (pain, temperature and crude touch), N. oralis (cutaneous sensation of oral mucosa) and N. interpolaris (tooth pulp pain). Second order fibers arising from these sites then cross the midline and ascend to synapse at the thalamus, from which thalamocortical projections then pass to those cortical areas concerned with oro-facial sensation and its appreciation. (86-89)

### **Neurophysiological techniques for recording orofacial pain**

Somatosensory evoked potentials (SEP)

*The trigeminal SEP (TSEP) waveform :*

The essential features of TSEP are the following sequence of waves. N13, P20 and N27. Some studies have also observed much earlier events, denoting N5 and P9 (90-92). The peak event at 20 ms has been noted as the most consistently obtained and the most

clinically used (93,94). The P20 wave is the first consistent sign of concerted cortical activation. Beyond 30 ms the Evoked potential, is subject to other influences such as efferent and limbic activity and memory recall, making the behavior and morphology of the wave form more complex to interpret.

These studies have shown that TSEP can be recorded by stimulation of peripheral branches of the trigeminal nerve. The site of stimulation is usually the oral cavity. The most favored being the lips or gums because of their relatively large sensory receptor representation in the cortex. The infraorbital nerve at the infraorbital foramen or the mentalis nerve as it emerges from the mandibular foramen is the other sites. These

however may show muscle artifacts on stimulation and may require the nerve to be pierced by a needle. Certain areas of scalp, which overlie the central gyrus, have been shown to be good recording sites for detecting TSEP. Reference electrodes are placed in the mid frontal position (Fpz). Positions C<sub>5</sub> and C<sub>6</sub> that overlie the facial area of somatosensory cortex are the most popular sites for active electrode (95).

Pain induced changes in TSEP could be observed on stimulation of tooth pulp. These pain-induced changes could further be studied in different diseased conditions, metabolic disorders in patients.

#### Clinical applications of TSEP

There is still much to be elucidated about some features of the trigeminal somatosensory evoked potentials (TSEP), particularly the early events. However, there are a number of instances where they have proved to be valuable in the assessment of certain conditions. Their use and further exploration is advocated in these conditions (96-98)

For example a significant increase in the latency of the P20 event has been taken to indicate a compressive lesion in trigeminal neuralgia, and this feature distinguishes those patients most likely to benefit from surgical correction. (99).

The abolition of peaks N5 and P9 and the normalisation of the latency of the N13 peak has been taken to indicate the success of the treatment by thermocoagulation of the trigeminal ganglion. (100).

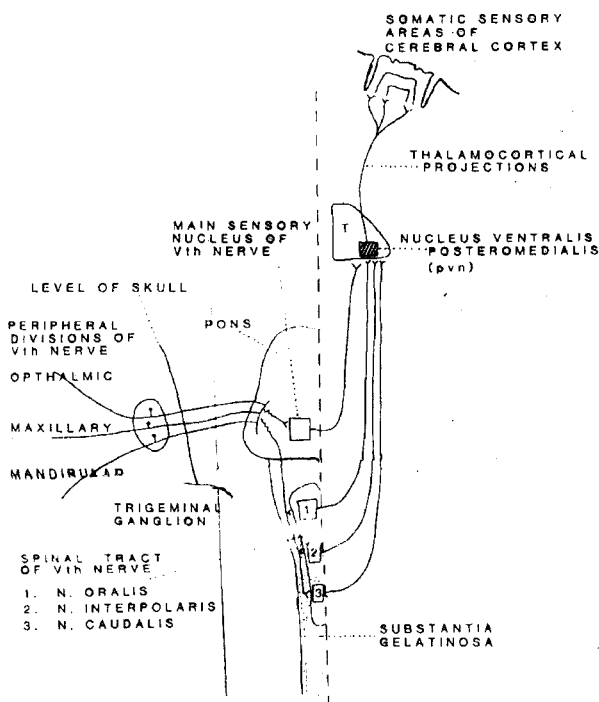


Fig. 4: Summary of the central connections of the Trigeminal Nerve.



Similarly, preservation and improvement of tactile sensibility following surgical procedures may be monitored using TSEP. Impairment of sensibility may be indicated by reduction in amplitude, latency delays and even abolition of the response (101).

A condition in which a patient experiences an exaggerated response to noxious stimuli is termed as Anaesthesia dolorosa (AD). It usually occurs postdental surgeries, in trigeminal tumors and post-herpetic neuralgias. Increased amplitudes of TSEP beyond 50ms in AD is a diagnostic indicator.

This is an example where the subjective pain sensation may be objectively assessed by the dental clinician using TSEPs.

#### **Physiological basis of pain relief: clinical applications**

##### *Control of pain*

One of the most important aspects of practice of dentistry is the control or elimination of pain. Pain has been so closely associated with dentistry that pain and dentistry have become almost synonymous. (76)

Following are the methods of pain control:

- 1) Removing the cause
- 2) Blocking the pathway of painful impulses e.g. Local anaesthetics
- 3) Raising the pain threshold e.g. aspirin and other pharmacological agents.
- 4) Preventing pain reaction by cortical depression e.g. general anaesthesia

- 5) Using psychosomatic methods e.g. hypnosis, faith healing.

The first two methods affect pain perception, the last two affect pain reaction, the third affects both.

#### **Previous/old techniques**

Across studies results suggested that acupuncture, biofeedback and relaxation were comparable to conservative treatment (for example an intraoral appliance) and warranted further study. There were no studies found that conducted randomised clinical trials that tested the effects of homeopathy, naturopathy, chiropractic, massage, meditation, yoga or herbal medicines for chronic facial pain. Significant gaps in the scientific basis limit the accuracy with which dental professionals can guide their patients regarding Complementary alternative medicine approaches used to treat chronic facial pain (101).

#### **Acupuncture**

In Classical Chinese Medicine it is postulated that a vital force or life energy (chi) flows through the body in channels or meridians.

Disease is associated with disturbance of this flow, but fortunately, the fault can be corrected by inserting one or more needles into the meridians concerned.

#### **Scientific basis: mechanisms of Acupuncture**

Electropuncture has been found to produce analgesia in various chronic pain syndromes of musculoskeletal origin (102).

This effect is due to activation of the peri-aqueductal matter which is connected to the descending inhibitory pathways of the lower brainstem. (103)

This activation of the per-aqueductal grey matter releases endogenous opiod peptides on their binding sites, resulting in an inhibition of the inhibitory neurons and a subsequent disinhibition of the output neurons to the nucleus raphe magnus and nucleus raphe dorsalis. From these raphe nuclei of the lower pons and medulla, one pathway spreads down to the dorsal horn of the spinal cord where incoming pain signals are inhibited and another spreads upwards and releases 5-HT in forebrain structures. Thus., with electropuncture both descending and ascending inhibitory pathways are involved in pain control (104)

In the study group for electropuncture, sterilised acupuncture needles are introduced into the points selected according to traditional Chinese channels and collaterals. (105,106)

Acute pain is sometimes proportional to the extent of injury, but the contribution of psychological factors reveal complex relationships that are profoundly influenced by fear, anxiety, cultural background and the meaning of the situation to the person (107). Various workers using evoked potential have reported electrophysiological correlates of acupuncture (41). These analgesia studies suggest interaction of other sensory afferents with specific pain pathways in brain, relieving pain.

### **Recent developments**

Some workers have reported that the application of electrical stimulation to the pituitary gland (PG) has produced dramatic relief of intractable pain caused by advanced cancer (108,109). Electrical stimulation of the pituitary gland was followed by suppression of tooth pulp evoked potentials (110). The Pituitary Inhibitory system is an entirely new picture of the mechanism by which electrical stimulation of the PG results in pain relief and consists of rendering the hypophyseal system hyperactive, which in turn antidromically exerts an inhibitory influence on the pain pathway in the brain (111).

### **Pharmacology and pharmacotherapeutics**

The narcotic Fentanyl reduces the sensory intensity but not the unpleasantness of painful pulp sensation (112). In contrast, anxiolytics such as Diazepam reduces affective discomfort rather than sensory-intensity qualities of the experience. Similarly placebo medication has an impact on unpleasantness rather than on sensory qualities of painful events.

There is also sufficient evidence of efficacy of carbamazepine in trigeminal neuralgia, also for baclofen and lamotrigine. In Temporomandibular disorders (TMD), there is evidence of a moderate effect of muscle relaxants/ tranquilisers (113).

Recent advances in knowledge of the neural processes underlying pain in the face and mouth reveal a remarkable degree of

plasticity following injury or inflammation of craniofacial tissue. Insights into mechanisms involved in the transmission and modulation of nociceptive signals in the brainstem hold promise of the development of new or improved therapeutic procedures for the relief of pain (114).

#### **Future trends and future therapeutic directions**

A promising approach is the use of corticotrophin-releasing hormone antagonists. This is based on several undergoing trials on chronic facial pain patients with antidepressants (115,116). It has been postulated that hyperactivity of the HPA axis in-patients with fibromyalgia correlates with depression.

This leads us on to the hypothesis that perhaps facial pain occurs in susceptible individuals who have an underlying abnormality of stress hormone response resulting in higher cortisol levels. Recent data indicate very high anytime cortisol levels in patients with facial pain indicating pathology in the hypothalamic Pituitary axis (HPA) (117).

As yet, there are no data available on

whether high cortisol levels persist in facial pain patients treated with antidepressants and the mechanism of antidepressants to modulate the Hypothalamic Pituitary axis activity and increase glucocorticoid is still unknown. (118)

#### **Tackling pain at the source: new ideas about nociceptors**

P2X receptors are a family of ligand gated ion channels responsive to ATP, and seen subtypes that form homometric or heterometric channels have been identified (119). In the spinal cord ATP acts presynaptically to regulate transmitter release and involves NMDA receptor mechanism. (120-123)

Recent studies have provided evidence of P2X mechanisms influencing nociceptive transmission in the trigeminal system. (119,124). These research studies indicate application of selective antagonist for example TNP-ATP (2'-(or 3'-) O-trinitrophenyl-ATP) may reversibly attenuate the perception of nociceptive stimuli to the tooth pulp. On application there is a decrease in neuronal mechanoreceptor field and responses to innocuous and noxious mechanical stimuli (120,125).

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