TRABAJO DE FIN DE GRADO

Grado en Odontología

THE ROLE OF GABA RECEPTORS IN OROFACIAL PAIN

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1. Summary

El dolor es una experiencia sensorial extremadamente importante que advierte a la persona de una posible lesión. El dolor orofacial es uno de los más intensos que se experimentan debido a la abundancia de receptores sensoriales en la piel, las mucosas, los músculos y los ligamentos de la cara. La Neuralgia del Trigémino, los Trastornos Temporomandibulares y la Odontalgia Atípica producen un dolor intenso y que, aunque tienen diversos tratamientos, pueden seguir produciendo dolor crónico y afectar a la calidad de vida. Los ácidos gamma-aminobutíricos (GABA, por sus siglas en inglés) son los principales neurotransmisores inhibidores del cerebro humano y de la médula espinal, responsables de la mayoría de las actividades del sistema nervioso central. El GABA puede aumentar o reducir la transmisión y la percepción del dolor. Los objetivos principales de este trabajo es investigar la importancia de los receptores GABA en el dolor orofacial y explorar diferentes ejemplos de dolor orofacial. Los objetivos secundarios son comprender la importancia del alivio del dolor, describir los distintos tipos de receptores GABA y explorar cómo afectan los distintos fármacos a los receptores GABA y los resultados clínicos que producen. La estrategia de investigación se basó en una revisión bibliográfica de los artículos disponibles en las bases de datos electrónicas. Se realizó una búsqueda sistemática de artículos publicados después de 1990. La estructura y la función de los diferentes receptores GABA influyen en el modo en que se transmite y percibe el dolor. Diferentes fármacos, agonistas o antagonistas, se unen selectivamente a las subunidades de GABA A y GABA B, lo que provoca una respuesta excitatoria o inhibitoria en la regulación y la percepción del dolor a través de diferentes vías.

2. Abstract

Pain is an extremely important sensory experience that warns the person of impending injury. Orofacial pain is one of the most intense pains experienced due to the abundance of sensory receptors in the skin, mucosae, muscles and ligaments of the face. Trigeminal Neuralgia, Temporomandibular Disorders and Atypical Odontalgia produce severe orofacial pain and although they have a variety of treatments, can still produce chronic pain and affect quality of life. Gamma-aminobutyric acids (GABA) are the primary inhibitory neurotransmitters in the human brain and the spinal cord that are responsible for the majority of the activities of the central nervous system. GABA can enhance or reduce pain transmission and perception. The main objectives are to investigate the importance of GABA receptors in different examples of orofacial pain. The secondary objectives are to understand the importance of pain relief, to describe the different types of GABA receptors and to explore how different drugs affect the GABA receptors and the clinical results they produce. The research strategy was based on a literature review of papers available in electronic databases. A systematic search for papers published after 1990 was performed. The structure and function of the different GABA receptors influence how pain is transmitted and perceived. Different drugs, either agonists or antagonists selectively bind to the subunits on GABA A and GABA B, which causes an excitatory or inhibitory response in the regulation and the perception of pain through different pathways. Even though a description is offered about the GABA-specific pharmacology, no evidence was found of drugs developed specifically to treat orofacial pain.

3. Index

4. Introduction

4.1, Pain

4.1.1. Definition of pain

According to the International Association for the Study of Pain, pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, an actual or potential tissue damage". [1] Pain is important for many reasons, the primary one being to alert the person of a problem or possible disease, protecting them from harm and preventing injury. It is ultimately a survival mechanism.

Determining the aetiology, characteristics, location and the intensity of pain is difficult because it is subjective as everyone has a different perception of pain. It depends on a few factors, including but not limited to, the person's individual pain tolerance, the intensity of the stimulus, their emotional state and the conditions surrounding the person at the time of the occurrence of pain. [2] Regardless of these factors, pain is an uncomfortable feeling for anyone, although chronic pain is especially unpleasant and affects how a person lives by reducing their quality of life psychologically, physically and socially.

4.1.2. Types of pain: Acute and Chronic

Acute pain is primarily caused by a nociceptive reaction to an injury or disease. It normally presents as a single, sharp pain that disappears almost immediately after it appears. [3] The mechanism by which the perception of pain and its response is produced is fast and ultimately informs the person of impending danger. The body therefore reacts by causing a protective response to acute pain. To give a few

examples, acute pain can be generated by the intense heat produced by a flame, a cut from a sharp object or a broken bone.

On the other hand, chronic pain is produced by an injury or disease that occurs over a prolonged period of time where the central nervous system has become accustomed to the repeated injury or stimulus due to the desensitization of nociceptors. [3] This is therefore not a protective response anymore and does not have any risk-benefit consequences. Chronic pain is characterised by having a duration of more than three months and one of the problems with chronic pain is that there may not be any definitive end-date to it. [2] In some cases the pain can only be managed on a day-to-day basis and not be successfully treated. It is the common issue of causes versus symptoms. Due to the continuous nature of chronic pain, patients believe that there may be no cure which often leads to depression and other mental health issues. Consequently, in addition to pharmacological and therapeutic methods, psychological assistance may be beneficial and necessary.

4.1.3. Pathway and mechanism of pain

Pain is produced by the stimulation and irritation of the receptors located in the brain and different parts of the body. The orofacial pain receptors are found in the skin, muscles and ligaments surrounding the mouth and face as well as in the dental pulp. [3] These pain specific receptors are called “nociceptors”, which are primary afferent neurons going to the brain with nerve endings in the orofacial tissue. [4] The nociceptors are designed to be a warning to the patient of impending pain and danger.

Aδ and C nerve fibres innervate the orofacial region and send different types of pain signals to the brain. [3] Aδ fibres provide and transmit an immediate protective response because the impulse is sent at a rate of 20 metres per second to the central nervous system due to their myelination. A myelin sheath is a fatty sheath wrapped around certain nerve fibres, which provide a faster rate of transmission of the pain signals. [2,3] Essentially, Aδ react to acute pain as they produce a sharp, intense and specific pain. One of the nociceptors specific to Aδ fibres are mechanoreceptors, which detect touch and pressure stimuli. [5]

The second fibre, the C fibre, does not provide an immediate protective reflex. It instead responds to persistent pain and provides a secondary reaction to the Aδ fibres. [3] For instance, if a person cuts their hand, they will automatically feel a sharp pain delivered by the Aδ fibre and after a while their hand will start to ache and throb for a prolonged period of time. This subsequent pain is transmitted along the C fibres. Without myelination and because they have a smaller diameter, the transmission speed of the action potential in C fibres is much slower than Aδ, occurring at a rate of 0.5 to 2 metres per second, rather than 20 metres per second with the Aδ fibres. The pain brought about by the C fibre is dull, pulsating and continuous with a diffuse distribution. [2,5]

Pain is a reaction to a stimulus, which can be chemical, biological, thermal, electrical or mechanical. [3,6] The strength of the stimulus needs to be intense enough to overcome a threshold, providing electrical impulses, which creates a communication with the dorsal horn of the spinal cord and brainstem. The thalamus, which is located in the central part of the brain, is where pain is registered and allows the person to perceive it, feel it and produce a response. [2]

Depending upon the area of the body where the pain is inflicted, the pain signal is then sent to different parts of the brain and the spinal cord. In the case of orofacial pain, it is transmitted from the orofacial tissue to the spinal and principal trigeminal nucleus in the brainstem. [5]

The ascending pain pathway carries sensory information from the stimulus in the body upwards to the brain. An injury is detected by nociceptors which transmit all the information about the pain to the spinal cord, medulla, thalamus and the cortex, which are part of the higher centres of the brain. [6] The descending pathway modulates the perception of pain and provides motor signals from the midbrain and brainstem to the reflex organs causing a response. [7] The descending pathway is also capable of controlling and inhibiting pain signals at the spinal cord, acting as an "endogenous analgesic system" [3,4,8]

"The Gate Control Theory of Pain" proposed in 1965 by Melzack and Wall, explains the mechanism for how pain-related signal transmission is decreased by inhibitory GABA interneurons in the substantia gelatinosa of the dorsal horn. [9-11] This mechanism can work as a "gate" to stop the nociceptive signal from reaching the brain. [4, 12] At the dorsal horn of the spinal cord, inhibitory interneurons release neurotransmitters including GABA. GABA then binds to the presynaptic neuron and inhibits the release of other pain stimulating neurotransmitters called glutamate and substance P, preventing a nociceptive response. [3,12-14] Interestingly, the "pain gate" is opened upon an important noxious stimulus or by an interfering signal. This happens thanks to collateral branches from other pathways that modulate the activity of the GABA-ergic interneuron.

4.2. Types of orofacial pain

Orofacial pain is confined to the area of the face, including the oral cavity and the mandible. It has a prevalence of up to 22 to 26% in the general population, with 7 to 11% experiencing chronic pain. [15] Its primary pathology is due to odontogenic pain and the secondary pathologies are non-odontogenic, which includes musculoskeletal, neuropathic and neurovascular diseases. [15]

Odontogenic pain, also known as dental pain, is produced specifically by damage to the teeth and their surrounding structures, including the mucosa, gingiva, maxilla, mandible and periodontal membrane. [16] It can be caused by dental caries, periodontal disease, cracked tooth syndrome and alveolar osteitis and it is generally experienced by aching pain with an acute onset. [16] Prolonged suffering of pain can cause it to spread from the initial site to a wider area of the face and therefore impact a patient's quality of life. Pain can be relieved by dental treatment and medication, including analgesics and antibiotics in the case of an infection.

Non-dental related pain is referred to as non-odontogenic and can be localised, intraoral or extraoral. Diseases include burning mouth syndrome, glossodynia, stomatodynia, oral ulcers and lichen planus. [17] Often, non-odontogenic pain is mistaken for odontogenic pain, which can result in unnecessary dental procedures, including extraction of teeth and surgery.

Clinical presentation in the form of musculoskeletal disorders includes Temporomandibular Disorders (TMDs). Examples of TMDs include disc displacement, osteoarthritis and subluxation of the temporomandibular joint. [18] TMDs are definitively diagnosed using neuroimaging devices, mainly Magnetic

Resonance Imaging (MRI). This is considered to be the gold-standard to examine the disc and its surrounding structures. Treatment involves an occlusal splint, physiotherapy, acupuncture and pharmacotherapy with non-steroidal anti-inflammatory drugs (NSAIDs). [15]

Neuropathic pain is caused by "a lesion of the peripheral and/or central nervous system manifesting with sensory symptoms and signs". [15] One of the most common types of neuropathic pain is Trigeminal neuralgia. Trigeminal primary efferent neurons are involved in pain processing in the orofacial region and have their cell bodies located in the trigeminal ganglion. [3] It is mainly produced by the compression of the trigeminal nerve, which runs throughout the orofacial region although there are also idiopathic forms. Neuralgia is the "pain in the distribution of a nerve or nerves." [18] Classical Trigeminal neuralgia is characterised by unilateral, sudden, sharp and agonising pain. [15,19,20] Other examples of neuropathic pain include Glossopharyngeal neuralgia, burning mouth syndrome and anaesthesia dolorosa, which is also known as post-traumatic trigeminal neuropathy. [17]

Persistent idiopathic facial pain is also known as atypical facial pain. Although it is idiopathic, it is considered to be the second most frequently occurring neuropathic pain. It can be differentiated from Trigeminal Neuralgia by the fact that the pain of atypical facial pain is constant and is spread over a larger surface area. Whereas Trigeminal neuralgia is only diffused across the area of the face innervated by the Trigeminal nerve. [13] Atypical facial pain includes atypical odontalgia, which is specific to the hollow site of a tooth after its extraction.

4.3. GABA

Gamma-aminobutyric acids, mainly known as GABA, are the primary inhibitory neurotransmitters in the human brain and the spinal cord. [6,11,14] They are responsible for the majority of the actions of the central nervous system. The GABA neurotransmitters are activated by interneurons in the dorsal horn of the spinal cord after an intense stimulus causes a nociceptive response. [3,6]

GABA has the structure of an amino acid and is referred to as an amino acid neurotransmitter. Glutamate, which is another amino acid neurotransmitter, synthesises GABA in a decarboxylation reaction catalysed by the enzyme glutamic acid decarboxylase. [12]

Nearly half of all synapses in the brain express some kind of GABA receptor. [4] Ultimately, GABA reduces the activity of the central nervous system. As GABA is an inhibitory neurotransmitter, when it interacts with the receptor of a neuron, it makes the neuron less likely to generate an action potential. If such a neuron participates in the nociceptive pathway, GABA activity inhibits a pain response. [10]

There are a number of categories and subcategories of GABA including GABA A, GABA B and GABA C. Currently there is not enough information or studies on the function and structure of GABA C. In addition, there is no evidence to suggest that GABA C receptors are involved in pain transmission. [12]

4.3.1. GABA A

The GABA A receptor has a complex structure. It is made up of 5 subunits which are arranged both extracellular and intracellular. The sub-units are arranged around a central Chloride pore. [6,21]

GABA A receptors are ionotropic, meaning that they are GABA-gated chloride specific channels. Upon transmitter binding, GABA A causes the opening of an associated ion channel that is permeable to Chloride ions. The activation of the GABA A receptor causes an influx of Chloride ions into the neuron producing hyperpolarization. This causes an inhibitory postsynaptic potential and decreases the likelihood of generating action potentials. [10]

A stimulus causes an action potential to be produced in the presynaptic neuron, which causes Calcium ions to enter through the voltage-gated calcium ion channels. The Calcium ions cause vesicles containing the neurotransmitter GABA to fuse to the presynaptic membrane and release GABA. GABA then travels across the synaptic cleft and the GABA binds to the target receptors present on the postsynaptic membrane. The binding of GABA to the postsynaptic membrane causes the Chloride ion channel to open and an influx of Chloride ions makes the postsynaptic membrane negative and inhibits further action potentials. [7,10]

GABA A has multiple independent neurotransmitter and drug binding sites, including ones for Benzodiazepines, GABA, Barbiturates, Ethanol, anaesthetic steroids and volatile anaesthetics. [6] All these drugs are positive modulators of GABA and

increase its effect. Benzodiazepines produce sedation and muscle relaxation, while Barbiturates have anti-epileptic properties. [21] Alcohol and anaesthetics produce sedation and relaxation as well. Located between the alpha and beta subunits is the GABA binding site, whereas between the gamma and alpha subunits is the Benzodiazepine binding site. Several of the newer hypnotics are selective of the binding site and they tend to have a more hypnotic effect with less sedative effect. Zolpidem is an example of one of these newer hypnotics. [22]

4.3.2. GABA B

GABA B receptors are metabotropic, meaning that the receptors act through G-proteins to activate and open Potassium ion channels, allowing positively charged Potassium ions to flow out of the neuron, again making it more negative and causing hyperpolarization and an inhibitory postsynaptic potential. The actions of GABA are finalised when GABA transporters, which are proteins, transport GABA from the synaptic cleft into GABAergic neurons. [12]

GABA B receptors play a part in many vital neurological functions in the human body by regulating pain signals, either by alleviating pain or causing hypersensitivity to pain. [6] They are heterodimeric receptors, with two transmembrane domains: GABA B1 and GABA B2. [6,14] They are coupled with G-proteins and are widely distributed throughout the central and autonomic divisions of the peripheral nervous system. [6] Around half of GABA B receptors are present at the terminal of nociceptors in the superficial dorsal horn. [4] This proves just how important of a role GABA plays in the perception of a stimulus.

Instead of the Chloride ion channel function described for GABA A, GABA B works by activating Potassium ion channels and inhibiting Calcium ion channels. GABA will bind to GABA B1, which will produce an allosteric change in the GABA B2 subunit. This subunit is coupled to the G protein, which activates adenylyl cyclase, which causes the changes in the Potassium ion and Calcium ion channel function. [6,12,14]

4.3.3. Pharmacology and GABA

Due to GABA's potential to affect neuronal transmission, some drugs have been invented in order to increase or decrease its activity. These drugs produce different effects depending on whether they are an agonist or an antagonist of GABA. These effects include anxiolytic, anticonvulsant, sedative, amnesic and muscle relaxation. [6,23]

GABA A and GABA B receptors have independent target sites for drugs that alter the neurotransmitter function and can produce different effects. For example, the site for benzodiazepines and barbiturates is only located on the GABA A receptor. There is no site for benzodiazepines on the GABA B receptor. [24] However, both receptors each have a site specifically for an endogenous GABA agonist. By acting as an endogenous agonist of the GABA receptor, GABA itself can attach to the GABA target receptor, causing positive allosteric modulation and decreasing the perception of pain. [11,14]

GABA-related medications have the potential to inhibit as well as facilitate pain impulses. An allosteric modulator is when a drug, for example, Benzodiazepine, will bind to an allosteric site, meaning it will bind to a site that is not a GABA site and then changes GABA's response to the stimulus. [11] A positive allosteric modulator is an agonist and so enhances the affinity of the receptor to GABA, thereby decreasing the perception of pain. A negative allosteric modulator is an antagonist of GABA and therefore causes a decrease in the action of the neurotransmitter leading to hyperalgesia. [3]

Examples of positive allosteric modulators include Benzodiazepines, Barbiturates, muscle relaxants, Alcohol, Anaesthetic drugs, for example, propofol, and Etomidate. These are all agonists of GABA and so increase its effect. [6,11]

Negative allosteric modulators include Flumazenil, Saclofen and Bicuculline. [6]

5. Objectives

The aim of this literature review is to evaluate the importance of orofacial pain modulation in relation to the GABA pathway.

Main objectives:

a. To investigate the importance of GABA receptors in orofacial pain

b. To explore different examples of orofacial pain

Secondary objectives:

a. To understand the importance of pain relief

b. To describe the different types of GABA receptors

c. To explore how different drugs affect the GABA receptors and the clinical results they produce

6. Methodology

The research strategy was based on a literature review of the scientific and medical papers, books and documents available in various electronic databases. The databases searched were as follows;

1. Mendeley
2. Pubmed
3. Medline vía Biblioteca Dulce Chacón
4. ResearchGate
5. Google Scholar
6. NCBI (National Center for Biotechnology information)

There followed a systematic data search for papers published after 1990 because of the importance of the research performed then and the comprehensive consideration of GABA receptor physiology and pharmacology. Consequently, the date range in this study is from 1990 to 2021.

A number of different search strategies were used and the most effective chosen was the Boolean technique. The keywords used were:

1. GABA receptors
2. Orofacial pain
3. Mechanism of GABA receptors
4. Mechanism of pain
5. Drugs specific to GABA

Strict inclusion and exclusion criteria were used to ensure the information used was relevant and scientifically accurate. These criteria included not only the date 1999 to 2021 criterion but also once the results of the keyword searches for GABA receptors, orofacial pain, mechanisms and drugs had been completed, the analysis of these elements could be conducted.

7. Results and Discussion

7.1. Orofacial pain definition

Orofacial pain is one of the most intense pains experienced, because there are so many pain receptors in the face compared to the rest of the human body. In addition, the muscles in the orofacial region are some of the most active muscles, constantly used for “chewing, swallowing, speech production, communication and personal expression”. [20]

It is often difficult to diagnose patients with orofacial pain, because there may be no physical signs and because the symptoms are subjective and dependent upon each patient's individual susceptibility. Everyone experiences pain differently, depending upon their own pain threshold level. For example, a patient can become more tolerant to pain if they have experienced significant pain during their lifetime.

“Neuropathic pain arises from peripheral and central changes in neuronal function that are perceived as persistent pain and sensory abnormalities”. [20] Extraoral and intraoral examination are crucial in the diagnosis of orofacial neuropathic pain.

In the case of a neuropathic injury, for example, glossopharyngeal neuralgia, there is an alteration in the GABAergic functioning. Presynaptically, the voltage-gated calcium ion channels are inactivated, causing a depolarisation of the neuron. [14]

Exogenous GABA agonists decrease the sensation of pain, while antagonists can produce hypersensitivity to pain. Some studies have experimented in mice to remove GABA B receptors, which in turn led to hyperalgesia. [4,6] In a context of neuropathic

injury, for example in chronic Trigeminal Neuralgia, there is a decrease in the number of GABA neurotransmitters which produces hyperalgesia. [13]

In chronic neuropathic pain, sensitization can occur over a prolonged period of time. This is due to the reduction of GABAergic activity and the decrease of its inhibitory effect. [14] The exact method by which this downregulation occurs is still unknown. Trigeminal neuralgia is an example of this chronic neuropathic pain in which sensitization can occur. [3,13]

7.2. Types of orofacial pain

7.2.1. Trigeminal neuralgia

"Trigeminal neuralgia is the most common type of neuropathic pain of the stomatognathic system" [15] as it annually affects 4 to 13 per 100,000 people and the incidence increases with age. [19]

It is defined by The International Association for the Study of Pain "as a sudden usually unilateral severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve." [17]

The trigeminal nerve is located in the pons and innervates the skin, mucous membranes and muscles in the head. It divides into three main branches:

1. The ophthalmic nerve (V1): This further divides into 3 branches: the frontal, nasociliary and lacrimal nerve. They innervate the forehead, cornea, conjunctiva, iris, lacrimal gland, the frontal sinus and the upper part of the nasal cavity.

2. The maxillary nerve (V2): This nerve innervates the maxillary sinus, the nasal cavity, maxillary teeth and its mucosa and the palate.
3. The mandibular nerve (V3): This innervates all the muscles of mastication, the temporomandibular joint, the mandibular teeth and its mucosa and the anterior two thirds of the tongue. [25]

The pain is triggered by “chewing, talking, brushing teeth, cold air, laughing, light touch, smiling or any other stimulation of trigger-points around the nose and mouth”. [19,20] Regardless of intensity of the chewing, talking, brushing teeth and so on, these will produce severe pain lasting from seconds to minutes.

Although the exact cause of Trigeminal Neuralgia is unknown, The International Classification of Headache Disorders has classified it into two types: Type 1 and Type 2 [18]

Type 1 (TN1), also known as Classical Trigeminal Neuralgia is generally produced by the compression of the trigeminal nerve although it can also be idiopathic. Compression typically occurs on only one or two branches, most often being the second and third trigeminal branches. [19] Type 1 is characterised by a sharp, stabbing pain in the area of the face where the Trigeminal Nerve is located. [13,15]

Type 2 (TN2) is the secondary form, which can also be idiopathic or can be due to the compression of any other part of the face, including “an acoustic neuroma, meningioma, epidermoid cyst, aneurysm or AV malformation”. [20] This type of pain is not as intense, but presents with a dull, throbbing sensation. Although Type 1

produces an abrupt starting and stopping pain, Type 2 pain is continuous and diffused over a larger surface area. In addition, Type 1 presents a refractory period of a few minutes after the paroxysm. Type 2 does not have this refractory period. [20]

It is often difficult to diagnose if a patient has Trigeminal Neuralgia. Type 1 can be mistaken for trigeminal neuropathy, a systemic disease or odontogenic pain. Type 2 can be mistaken for a metabolic, endocrine or rheumatic disease. [15] Diagnosis is extremely important as a misdiagnosis of odontogenic pain can cause unnecessary dental procedures.

Neuroimaging is considered to be a crucial part of the diagnosis of Trigeminal Neuralgia when it is performed by a neurologist. Head Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA) can be used to detect if the Trigeminal nerve has been compressed. [19]

Classical Trigeminal Neuralgia can be treated in a variety of ways, including a Michigan stabilization splint, medication, surgery, acupuncture and botulinum toxin injections at the relevant trigger points in the face. [20]

In the case of pharmacological relief, the medication of choice is Carbamazepine, prescribed in doses of 100 to 200 mg twice daily. If the patient continues to feel intense pain, the dose can be increased to 300 to 500mg. Oxcarbazepine can also be used if Carbamazepine is ineffective. Oxcarbazepine is given in doses of 600mg daily taken at intervals as prescribed throughout the day. The dose can be increased

every third day to 900mg per day. If Carbamazepine and Oxcarbazepine do not work, then Baclofen or lamotrigine are used as alternatives. There have been trials using other drugs, for example Clonazepam, Gabapentin and Phenytoin although they have not been tested in a large enough group of people to produce definitive results. [19]

If these various types of medication are not successful, the neurologist can recommend to the patient to undergo surgery. Some types of surgical procedures that they may suggest might include microvascular decompression or alternative ablative procedures such as rhizotomy with radiofrequency thermocoagulation, mechanical balloon compression, chemical glyceryl injection, radiosurgery, peripheral neurectomy and a nerve block. [17,19]

7.2.2. Temporomandibular Disorders (TMD)

The temporomandibular joint (TMJ) is synovial and is articulated by the condyle of the mandible and the mandibular fossa of the zygomatic arch forming a hinge joint. [18] In between these two structures is a biconcave articular disc, which moves in synchronicity with the mandible's movements. A TMD occurs when there is a disc displacement, osteoarthritis or subluxation of the TMJ.

The most common cause of musculoskeletal pain in non-odontogenic pain is a TMD. [17] It is characterised by pain in the muscles surrounding the TMJ, which include the muscles of mastication. The consequences which can occur are a limitation in movement of opening and closing of the mandible and potential noises produced by the TMJ. These noises are different depending on the type of disorder. A clicking or

popping sound indicates that the disc has been displaced whilst a crunching sound, also known as crepitus, suggests that the injury is linked to osteoarthritis. [17]

Secondary symptoms can include headaches and migraines. [17] It is important to diagnose and treat TMDs early on, as prolonged subjection to pain can increase the patient's stress and negatively impact the quality of their daily life. Making a definitive diagnosis of TMDs is primarily done by the use of an MRI, which provides and shows the medical personnel an enhanced image of the anatomy of the TMJ and the disorder it presents.

Therapies used to treat TMDs can include physiotherapy, pharmacotherapy, occlusal splints, psychological and surgical treatment as well as introducing a soft diet to the patient in order to reduce the stress on their muscles of mastication. [17]

It has been seen that Trigeminal Neuralgia can accompany TMDs, increasing the pain experienced by the patient. [15]

7.2.3. Atypical odontalgia

Persistent idiopathic facial pain, also known as atypical facial pain, includes all facial pain with unknown aetiology. Some researchers have hypothesised that it derives from neuropathic pain although the results aren't conclusive and have not been proven. [17] Atypical odontalgia, or phantom tooth pain, is experienced within the dentoalveolar tissues and occurs after extraction of a tooth, the roots or the dental pulp. It occurs in 3 to 6% of the population after receiving a root canal treatment, most often in the maxillary premolars and molars. [20] Symptoms experienced by the

patient include a pulsating, constant or sporadic pain in the extraction site over a long period of time. During this time, it is possible that the pain can disseminate to other areas of the face.

Although Atypical Odontalgia is generally idiopathic, it has been found that it can be produced by maxillofacial trauma and can be triggered by touching the area of the face where the tooth previously was. [20]

Diagnosis is often difficult, but it can be conducted by completing a thorough anamnesis, clinical examination and radiographs. There are still ongoing studies into the use of different medications to treat Atypical Odontalgia, although those currently prescribed include Gabapentin, Tricyclics, topical anaesthetics and Opioids. [26]

7.3. GABA

7.3.1. GABA A specific drugs

7.3.1.1. Agonists

The basic mechanism involved in the activation of the GABA A receptor is the binding of an exogenous or endogenous agent to a specific site on the GABA receptor. This then causes the central chloride pore to open up and an influx of Chloride ions rushes into the neuron, which further causes inhibition of the neurons causing a state of hyperpolarization. [6,10,12]

Benzodiazepines are known to be one of the main positive allosteric modulators of GABA A. They are used in patients with anxiety and can also produce effects such as anticonvulsant, sedative, partial amnesia and muscle relaxation. [4,21] Diazepam and Clonazepam are the primary benzodiazepines prescribed for nervous patients.

They bind to the GABA A receptor and “increase the frequency of GABA-gated Chloride ion channel opening in the presence of GABA” [24] thus enhancing the GABA inhibitory effect. Benzodiazepines have their own binding site on the GABA A receptor. By attaching to an individual binding site, Benzodiazepine will activate the receptor to increase the action of the neurotransmitter GABA.

Another important group of drugs that are agonists of the GABA A receptor are Barbiturates. Phenobarbital is an anti-epileptic, anticonvulsant drug and Thiopental is capable of inducing anaesthesia. [6,12] The Barbiturates group also has an individual binding site on the GABA A receptor. While Benzodiazepines work by increasing the frequency of the chloride channel opening, the Barbiturates work by increasing the Chloride channel opening time in order to increase the influx of Chloride ions into the neuron. At very high concentrations, Barbiturates can open the Chloride ion channel in the absence of GABA, which can be dangerous. [23,25,27]

If a patient takes Benzodiazepines for more than two weeks, there is a risk of tolerance as the GABA receptors downregulate. [6] This means that there are fewer receptors available on the surface of a neuron to cause a sufficient response. This will cause the patient to increase the amount and frequency of the Benzodiazepines that they are taking in order to achieve the same effect. The longer they are used, the more they downregulate the GABA receptors. When the patient decides to stop taking them, it can take months or years for the GABA receptors to upregulate back to normal levels. [14] Although Benzodiazepines are extremely effective, it can be very difficult for a patient to reduce the dosage or stop taking them altogether, because they have a tolerant and addictive effect. [4,6,12]

7.3.1.2. Antagonists

Bicuculline is an antagonist for the GABA A receptor and can increase the sensation of pain. It does this by increasing the response of Aδ and C fibres and preventing GABA A from functioning properly. [12] It competes with GABA for a binding site on the receptor and also decreases the mean “channel open times and the opening frequency.” [28] Scientists discovered by injecting Bicuculline into the spinal cord of rats that the neural response to a stimulus was prevented, which included the involvement of GABA A receptors. [6]

Flumazenil is a negative allosteric modulator and a GABA antagonist. It is useful in reversing anaesthesia and is used in the case of an overdose of Benzodiazepines or Zolpidem. [24] It reverses the effect of Benzodiazepines by competing with them at the same binding site on GABA A, thereby blocking the Benzodiazepine site. Although Flumazenil is effective in the reversal of both Benzodiazepines and Zolpidem, it will have no effect on Barbiturates. This is due to the fact that the binding sites for Flumazenil, Benzodiazepines and Zolpidem are located close together, but too far from the binding site for Barbiturates. [22]

7.3.2. GABA B specific drugs

7.3.2.1. Agonists

The target sites on the GABA B receptor are extremely important for the attachment of analgesic drugs due to their significant role in the pain processing and neurological functions.

Baclofen is one of the main examples of a GABA B agonist. [6,9] Baclofen is a neuralgic analgesic, antispasmolytic and muscle relaxant, used for multiple sclerosis and spinal cord injuries. [4,14] Studies have shown that by injecting Baclofen into the trigeminal ganglion, it has reduced algesic activity by preventing the downregulation of GABA B receptors and by decreasing the activity of Aδ and C fibres, providing analgesia. [3,4,14]

Baclofen is a paradoxical drug as it can produce hyperalgesia as well as antinociception. [6] The principal reason for this depends on the concentration of Baclofen. When injected with a lower dose, it prevents the interneurons in the dorsal horn of the spinal cord from releasing GABA, which in turn produces hyperalgesia. [3] On the other hand, a higher dose of Baclofen prevents other neurotransmitters being released from the nociceptors that block the painful response from being experienced. [12]

Baclofen has a short half-life of only two to four hours and does not cross the blood-brain barrier very well. [4] As a consequence, in order to produce an effect, Baclofen needs to be prescribed in high doses. This can be dangerous, because it can produce strong side effects such as drowsiness, disorientation, slurred speech, gastrointestinal problems, nausea and hypotension. [4,6] Another problem with Baclofen is that these high doses can lead to a patient becoming tolerant and

addicted to the drug. Due to these disadvantages, Baclofen should only be prescribed in severe cases of chronic pain and when first-line drugs are ineffective, or in combination with them. [6,14] Despite its limitations, the fact that Baclofen produces an antinociceptive response indicates the vital role that GABA B receptors play in pain reduction.

7.3.2.2. Antagonists:

Phaclofen, Saclofen and 2-Hydroxysaclofen are antagonists for the GABA B receptor, and they prevent the inhibitory action of GABA B receptors and therefore its antinociceptive response. [14,29] They are selective and compete with Baclofen for the binding site on the GABA B receptor. [6,12] 2-Hydroxysaclofen has the ability to competitively attach to the binding site ten times more strongly than Phaclofen [29] and Saclofen attaches two times more strongly than -2-Hydroxysaclofen. [30] The information regarding these drugs is very limited and from the research that was conducted, its relation to GABA is that of an antagonist.

8. Conclusion

Orofacial pain is one of the most severe types of pain experienced, due to the high number of sensory receptors in the orofacial region. It is mostly associated with chronic pain rather than acute pain and in most cases, there is no definitive cure.

Therefore, it is extremely important to find analgesics that reduce the pain and increase the patient's quality of life. Although there is pharmacotherapy that specifically targets the receptors of GABA in order to relieve pain, these medications tend to have severe side effects and can cause a patient to become tolerant and addicted to the drugs prescribed.

There are at present no drugs that exist specifically for orofacial pain treatment. With the multitude of past and ongoing experiments into the role of GABA receptors in the processing of pain, there is hope in the future for more specific analgesics without the current severe side effects. There are limitations to the experiments because, to date, they have principally been tested in rats rather than in humans.

There are and have been many experiments and studies into the function and mechanism of GABA receptors relating to the perception and communication of pain in the human body. GABA is not just associated with the processing of orofacial pain, but in many other neurological functions. There is still great debate and many hypotheses into the number of processes in which GABA is involved.

The success in analgesic activity in GABA agonist drugs proves that GABA has a significant involvement in pain regulation and transmission. Their reaction to a stimulus and their location on neural pathways also prove how effective they are in inducing an antinociceptive or a nociceptive effect.

Scientists are consistently gaining an increasing amount of knowledge about GABA and therefore, there is hope for improved analgesics and hypnotics without their current issues of tolerance, addiction and hyperalgesia, which occur in the systemic administration for chronic pain.

9. Social Responsibility

By performing this bibliographic study, I have been able to understand the mechanism of pain and the involvement of many substances on a much deeper level. By learning the intricacy of how GABA is involved not just in the processing of pain but in many other vital functions in the human body, I feel I will be able to use this knowledge in my professional life to my and my patient's benefit. In addition, I have spent many hours researching scientific papers, and this has taught me how to read papers efficiently and quickly. Therefore, in the future this will allow me to update my knowledge in many areas of research, which will again be a benefit to my patients.

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Annex:

1.

Narrative Review

PAIN

The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises

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Abstract

The current International Association for the Study of Pain (IASP) definition of pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" was recommended by the Subcommittee on Taxonomy and adopted by the IASP Council in 1979. This definition has become accepted widely by health care professionals and researchers in the pain field and adopted by several professional, governmental, and nongovernmental organizations, including the World Health Organization. In recent years, some in the field have reasoned that advances in our understanding of pain warrant a reevaluation of the definition and have proposed modifications. Therefore, in 2018, the IASP formed a 14-member, multinational Presidential Task Force comprising individuals with broad expertise in clinical and basic science related to pain, to evaluate the current definition and accompanying note and recommend whether they should be retained or changed. This review provides a synopsis of the critical concepts, the analysis of comments from the IASP membership and public, and the committee's final recommendations for revisions to the definition and notes, which were discussed over a 2-year period. The task force ultimately recommended that the definition of pain be revised to "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage," and that the accompanying notes be updated to a bulleted list that included the etymology. The revised definition and notes were unanimously accepted by the IASP Council early this year.

Keywords: Definition, Terminology, Taxonomy, Task force, Revision, IASP

"Scientific and medical definitions are tools. Even when we recognize them as imperfect or provisional, awaiting replacement by an improved version, they perform work that cannot be accomplished by less precise instruments." David B. Morris[27]

1. Introduction

In 1978, after 2 years of deliberations, the International Association for the Study of Pain (IASP) Subcommittee on Taxonomy, chaired by Professor Harold Merskey and including representatives from diverse specialties, recommended definitions of "Pain Terms" to the IASP Council.[19] The subcommittee's recommendations, which were strongly endorsed by the then IASP president John J. Bonica and approved by the Council over 4 decades ago, included the current IASP definition of pain.[7] Pain was defined as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Box 1). In the accompanying editorial, John Bonica emphasized that the "development

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REVIEW ARTICLE

Assessment of pain: types, mechanism and treatment

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Abstract

Pain is the most common symptom of disease, which accompanies us from an early age. It is a protective mechanism to which the body responds to harmful stimulus. The definition of pain states that it is a subjective sensory and emotional experience. It is connected to the stimulus that it invokes and is also based on the observation of psychological interpretation of the phenomena taking place. Pain is individual for each person. Pain affects both our previous experience of pain and psychosomatic conditions, depending on the relationship between the psyche and the body. Pain is always an unpleasant sensation. The feeling of pain can be caused by irritation of pain receptors, which can be found in the skin, joints and many internal organs. The cause of pain may also be damage to the nervous system, both the peripheral nerves, brain and spinal cord. Pain can also occur without damage to tissues, although the patient refers to it (psychogenic pain). The process of pain is a complex phenomenon. Experience of pain depends on the strength of the stimulus, individual susceptibility and individual resistance to pain. Pain receptors are sensitive to mechanical, thermal or chemical stimuli. The operation of noxious stimulus to these receptors results in the processing into an electrical signal. This impulse is conducted by nerve fibress into the spinal cord and then to the brain. At this point, there is the realization that something hurts us. Pain is not only somatic in nature, associated with the condition of the body, but it is a multidimensional phenomenon. Therefore, in addition to the physiological process of pain, its subjective perception is also important, which is decided by the central nervous system. It consists of the emotional aspects: suffering and attitude towards pain and pain expression. A review of pain physiology is essential to fully understand the principles of pain management.

Key words

pain, pain treatment, health

INTRODUCTION

Pain is an unpleasant sensory and emotional feeling accompanying existing or impending tissue damage or referenced to such damage. Pain is the most common experience reported by patients, and patient anxiety is a form of warning signal. It is a sensual and perceptual phenomenon, which causes suffering and emotional state of risks connected with anxiety. Pain has many forms. It warns against damage to the body, which is important for avoiding injuries and consequently for survival. Pain not caused by acute injuries can be unpleasant for the patient, or it can alter a person's life, reduce the quality of life, and also have an impact on the patient's family. The word "pain" for the patient means disease and suffering, for the doctor it is a symptom, and for the physiologist it is a kind of feeling that has its own anatomical and physiological system which begins with the receptors and ends up in the brain cortex. Feeling is a physical sensation that can be confirmed by electrophysiological methods, but in practice it is only a subjective sensation. It's intensity and quality come under various internal and external factors; therefore, the same stimulus can be experienced differently in different circumstances, somatic and psychiatric conditions.

The way of receiving pain is very individual and varies from time-to-time in the same individual. The intensity of pain is difficult to measure and an individual's perception of pain depends on the individual's emotional state, circumstances under which the pain was acquired, and whether it is perceived as a threatening signal. The perception of pain depends on such factors as arousal, attention, distraction and expectation [1, 2, 3]. Before we realize that something hurts, there are a number of physiological processes in our body. Painful stimuli have to be passed quickly – in (milli) seconds. Acute pain warns about impending or ensuing danger while chronic pain causes the afflicted part of the body, such as an immobilized and unused limb, increasing the chance for recovery. A single, sharp stimulus to pain can disappear, and probably not leave a trail. Stimuli that are repeated, cause adaptive changes in the central nervous system and the activation of a number of systems, both supporting and inhibiting pain. In the spinal cord and the brain there occurs synthesis and the activation of various receptor systems, as well as synthesis of various compounds modifying the sense of pain. It is known that an important role in this process is played the glial cells. It is a very complicated process that can lead to the preservation the pain, even after the disappearance of the pain stimulus [4].

Pain can also be generated without receptors, from the peripheral and central nervous systems. This is always a pathological pain which arises due to damage to the nervous system, and has a different nature from physiological pain and clinical presentation. It is important to distinguish receptor pain – nociceptive, physiological pain from non-receptor pain – pathological, central and peripheral (Tab. 1).

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3.

Neurophysiology of Orofacial Pain

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Abstract

It is well known that unmyelinated C-fibers and small-diameter Aδ-fibers innervate the orofacial skin, mucous membrane, orofacial muscles, teeth, tongue, and temporomandibular joint. Peripheral terminals consist of free nerve endings, and thermal and mechanical receptors such as transient receptor potential (TRP) channels and purinergic receptors exist in nerve endings. Ligands for each receptor are released from peripheral tissues following a variety of noxious stimuli applied to the orofacial region and bind to these receptors, following which action potentials are generated in these fibers and conveyed mainly to the trigeminal spinal subnucleus caudalis (Vc) and upper cervical spinal cord (C1-C2). Neurons receiving noxious inputs from the orofacial regions are somatotopically organized in the Vc and C1-C2. The third branch (mandibular nerve) of the trigeminal nerve innervates the dorsal portion of the Vc, and the first branch (ophthalmic nerve) of the trigeminal nerve innervates the ventral part of the Vc; the middle portion of them receives the second branch (maxillary nerve) of the trigeminal nerve. Various neurotransmitters such as glutamate and substance P (SP) are released from primary afferent terminals and bind to receptors such as AMPA and NMDA glutamate receptors and NK1 receptors in Vc and C1-C2 nociceptive neurons. Further, noxious information from the orofacial region reaching Vc and C1-C2 is sent to the somatosensory and limbic cortices via the ventral posterior medial thalamic nucleus (VPM) and medial thalamic nuclei (parafascicular nucleus, centromedial nucleus, and medial dorsal nucleus), respectively, and finally, orofacial pain sensation is perceived. It is also known that descending pathways in the brain act on Vc and C1-C2 nociceptive neurons to modulate pain signals. Under pathological conditions such as trigeminal nerve injury or orofacial inflammation, trigeminal ganglion (TG) neurons become hyperactive, and a barrage of action potentials is generated in TG neurons, and these are sensitized a long time after the hyperactivation of

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4.

$GABA_B$ Receptors and Pain

Dietmar Benke

Contents

Abstract A substantial fraction of the human population suffers from chronic pain states, which often cannot be sufficiently treated with existing drugs. This calls for alternative targets and strategies for the development of novel analgesics. There is substantial evidence that the G protein-coupled $GABA_B$ receptor is involved in the processing of pain signals and thus has long been considered a valuable target for the generation of analgesics to treat chronic pain. In this review, the contribution of $GABA_B$ receptors to the generation and modulation of pain signals, their involvement in chronic pain states as well as their target suitability for the development of novel analgesics is discussed.

Keywords Chronic pain · $GABA_B$ receptor · Hyperalgesia · Inflammatory pain · Neuropathic pain · Nociception

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5.

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Leading article

Functional neuroanatomy of nociception and pain

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Abstract

Pain is a complex sensory state based on the integration of a variety of nociceptive inputs processed centrally through many parallel and overlapping neural systems. The traditional anatomical concept implies that nociceptive information is dominantly used to generate and regulate perception of pain through one major sensory pathway. It becomes recognized that experiencing the affective component of the pain is at least as important as perception. Also, nociceptive information is strongly influencing brain centers for regulating homeostasis. So, understanding neuroanatomical organization of central processing of nociceptive information is of great clinical importance. There is an attempt to simplify this complex set of interacting networks to a core set of brain regions or a generalizable pain signature. Herewith we wish to give a short overview of recent advances by presenting principles about neuroanatomical organization for processing various aspects of nociceptive inputs.

GENERAL NEUROANATOMICAL PRINCIPLES IN NOCICEPTIVE PROCESSING

Pain is the most distinctive of all the sensory modalities *(1)* but can be simply defined as the subjective experience associated with actual or potential tissue damage *(2–5)*. It serves an important protective function and warns to avoid or treat injury. The perception of pain is subjective and can vary greatly among individuals. Moreover, in the same individual an identical sensory stimulus can elicit quite distinct conscious responses under different conditions. This includes also psychological conditions, such as fear or anxiety that can significantly influence the experience of pain. So, more than most sensory modalities, the perception of pain is influenced by emotional state and environmental contingency, is dependent on experience, and varies so markedly from person to person *(6–16)*, and consequently remains notoriously difficult to treat .

Noxious stimuli, including tissue injury, activate nociceptors (from the Latin, noceo = to injure, hurt) which are present in peripheral structures and transmit information to the CNS: from the body to the spinal cord dorsal grey column, from the skin of the head to the spinal and principal trigeminal nucleus, and from the neck mucosa to the lower 2/3rd of solitary tract nucleus *(17–19)*. To generate perception of pain the information should continue ultimately to the cerebral cortex. From anatomical point of view it should be noted that nociception refers to the process through which information about peripheral stimuli is transmitted by primary afferent nociceptors to the spinal cord, brainstem, thalamus, and subcortical structures. For the experience of pain, activity of thalamocortical networks that process the information conveyed by pathways of nociception is needed *(20–26)* (Figure 1).

6.

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The Role of GABA in the Mediation and Perception of Pain

I. Chapter Overview

For nearly three decades efforts have been made to define the role of GABAergic transmission in the mediation and perception of pain. The anatomical distribution of GABA neurons and receptors, as well as the antinociceptive responses to $GABA_A$ and $GABA_B$ receptor agonists, is consistent with the notion that manipulation of this transmitter system may be of clinical benefit in the treatment of acute, inflammatory, and neuropathic pain. Contained in this report is a review of the data in support of this proposition, a discussion of disparate and contradictory findings, and a description of theories used to explain variation in the antinociceptive responses to GABAergic drugs. Particular emphasis is placed on interpreting the results in the context of the anatomical localization and function of GABA neurons as well as the molecular and pharmacological properties of GABA receptor subtypes. Included is a discussion of evidence suggesting

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A Brainstem-Spinal Cord Inhibitory Circuit for Mechanical Pain Modulation by GABA and Enkephalins

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SUMMARY

Pain thresholds are, in part, set as a function of emotional and internal states by descending modulation of nociceptive transmission in the spinal cord. Neurons of the rostral ventromedial medulla (RVM) are thought to critically contribute to this process; however, the neural circuits and synaptic mechanisms by which distinct populations of RVM neurons facilitate or diminish pain remain elusive. Here we used in vivo opto/chemogenetic manipulations and *trans*-synaptic tracing of genetically identified dorsal horn and RVM neurons to uncover an RVM-spinal cord-primary afferent circuit controlling pain thresholds. Unexpectedly, we found that RVM GABAergic neurons facilitate mechanical pain by inhibiting dorsal horn enkephalinergic/GABAergic interneurons. We further demonstrate that these interneurons gate sensory inputs and control pain through temporally coordinated enkephalin- and GABA-mediated presynaptic inhibition of somatosensory neurons. Our results uncover a descending disynaptic inhibitory circuit that facilitates mechanical pain, is engaged during stress, and could be targeted to establish higher pain thresholds.

INTRODUCTION

The brain has long been known to powerfully influence pain thresholds by modulating somatosensory information processing at the level of the spinal cord. This phenomenon, known as the descending control of pain (Basbaum et al., 2009; Porreca et al., 2002), underlies changes in pain thresholds as a function of mood, expectations, and internal states. For example, acute stress and expected pain relief can produce analgesia (i.e., stress-induced and placebo analgesia; Butler and Finn, 2009; Wager and Atlas, 2015), while chronic stress and anxiety can facilitate pain (Jennings et al., 2014), as observed during post-traumatic stress disorder or pain catastrophizing (Palyo and Beck, 2005; Quartana et al., 2009). Previous studies established that descending pain control utilizes neurons of the rostral ventromedial medulla (RVM), an ensemble of functionally related structures, including the raphe magnus and gigantocellular reticular nuclei (Fields et al., 1983a, 1983b; Marinelli et al., 2002; Zhuo and Gebhart, 1990). Classic extracellular recording experiments indicated the existence of several classes of RVM neurons projecting to the spinal cord: on-cells, off-cells, and neutral-cells (Fields et al., 1983a). On-cells are thought to critically contribute to descending pain control by facilitating nociception, presumably via glutamatergic neurotransmission and the excitation of primary afferent terminals and/or excitatory dorsal horn neurons (Heinricher et al., 2009). However, the molecular identity of on-cells is unresolved. Furthermore, the organization of RVM-spinal cord circuits, and mechanisms by which RVM neurons modulate neural activity and nociception at the spinal level, remains poorly understood.

The endogenous opioid system regulates nociception, which includes altering excitability and neurotransmission in the RVM and spinal cord (Basbaum et al., 1976; Heinricher et al., 2009). Exogenous opioid analgesics, such as morphine, act on mu opioid receptors (MORs) on on-cells to reduce pain facilitation and on MORs and delta opioid receptors (DORs) on dorsal root

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Current Opinion in Neurobiology

Descending modulation of pain: the GABA disinhibition hypothesis of analgesia

Benjamin K Lau and Christopher W Vaughan

Within the central nervous system, descending systems exist to endogenously modulate our perception of pain. Of particular interest is a descending pathway which projects via the midbrain periaqueductal grey (PAG) and rostral ventromedial medulla (RVM) to inhibit ascending nociceptive transmission at the spinal cord dorsal horn. This descending PAG–RVM system forms the circuitry that underlies the physiological phenomenon of stress-induced analgesia (SIA), which is mediated by parallel opioid and cannabinoid neurotransmitter systems in the PAG. At the cellular level, opioids and cannabinoids are hypothesised to activate descending analgesia through an indirect process of 'GABA disinhibition' — suppression of inhibitory GABAergic inputs onto output neurons which constitute the descending analgesic pathway. While there is much indirect evidence to support disinhibition, there are still questions regarding this model that remain unaddressed. Furthermore, there is growing evidence suggesting more complex models than originally proposed.

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Introduction

The perception of painful or noxious information serves an important function in detecting actual or potential tissue damage in the body. In doing so, it provides an 'image of well-being' [1]. Information about pain is conveyed via primary afferent nociceptors to the dorsal horn of the spinal cord, and then transmitted to the brain via a number of ascending pain pathways. This ascending nociceptive signal is modulated by a number of supraspinal descending pathways, which serve as an endogenous analgesic system. In this review, we discuss our current understanding of the cellular mechanisms underlying activation of descending analgesic pathways.

Descending PAG–RVM analgesic pathway

A particularly well-characterised descending pathway originates within the midbrain periaqueductal grey (PAG) and projects to the spinal dorsal horn via the rostral ventromedial medulla (RVM) (Figure 1a). Activation of this descending system, either from within the PAG, RVM or higher centres, elicits analgesia by inhibiting ascending nociceptive transmission at the spinal cord level [2•]. The descending PAG–RVM-spinal pathway is of particular interest for a number of reasons. The PAG and RVM are major sites of analgesic action by opioid and cannabinoid agents. In addition, they mediate the physiological phenomenon of stress-induced analgesia (SIA), which has parallel opioid and cannabinoid endogenous components within the PAG [3,4]. It is important to note that this function is part of a broader regulatory system that co-ordinates an organism's somatomotor, autonomic and behavioural responses to threat, stress and pain [5]. How pain and stress activate this descending pathway through the opioid and cannabinoid neurotransmitter systems has been the focus of much research dating back to the 1970s.

The 'GABA disinhibition' hypothesis of opioid analgesia

The early observation that analgesia can be evoked via electrical stimulation, or microinjection of excitatory amino acids (EAAs) into the PAG, indicated that antinociception is the result of direct excitation and activation of primary neurons which constitute the PAG–RVM descending pathway, that is, output neurons that project from the PAG to the RVM [6]. Confounding this notion, however, opioids have a direct inhibitory effect on neurons, yet also produce analgesia when microinjected into the PAG and RVM [7–9].

To account for this seemingly paradoxical excitatory effect of opioids in pain pathways, Basbaum & Fields proposed the 'GABA disinhibition' hypothesis of analgesia [2•]. This hypothesis was derived based on a number of *in vivo* neuropharmacological studies. According to the original hypothesis, tonically active GABAergic interneurons are present within the PAG and RVM, which release the neurotransmitter GABA, and act via $GABA_A$ receptors to inhibit spinally projecting output neurons (Figure 1b). It was proposed that opioids activate the PAG–RVM descending pathway by indirectly suppressing the inhibitory

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CLINICAL FOCUS: SNAPSHOT IN PAIN MANAGEMENT
REVIEW

Mechanisms and mode of action of spinal cord stimulation in chronic neuropathic pain

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ABSTRACT

Tonic spinal cord stimulation (SCS) has been used as a treatment for chronic neuropathic pain ever since its discovery in late 1960s. Despite its clinical successes in a subset of chronic neuropathic pain syndromes, several limitations such as insufficient pain relief and uncomfortable paresthesias have led to the development of new targets, the dorsal root ganglion, and new stimulation waveforms, such as burst and high frequency. The aim of this review is to provide a brief overview of the main mechanisms behind the mode of action of the different SCS paradigms. Tonic SCS mainly acts via a segmental spinal mechanism where it induces GABA-release from inhibitory interneurons in the spinal dorsal horn. Tonic SCS concurrently initiates neuropathic pain modulation through a supraspinal-spinal feedback loop and serotonergic descending fibers. Mechanisms of stimulation of the DRG as well as those related to new SCS paradigms are now under investigation, where it seems that burst SCS not only stimulates sensory, discriminative aspects of pain (like Tonic SCS) but also emotional, affective, and motivational aspects of pain. Initial long-term study results on closed-loop SCS systems hold promise for improvement of future SCS treatment.

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KEYWORDS
Spinal cord stimulation; pain modulation; tonic; burst; high-frequency; mechanism of action; dorsal horn; nociception; serotonin; GABA

1. Introduction

Spinal cord stimulation (SCS) is indicated as a treatment option for multiple chronic neuropathic pain syndromes, including failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), and diabetic polyneuropathy (PDPN) [1]. Conventional or Tonic SCS treatment requires the implantation of stimulation electrodes in the epidural space, placed on top of the dorsal column and at the level at which the nerve roots associated with the painful dermatomes enter the spinal cord. Shealy and colleagues [2] first introduced spinal cord stimulation in 1967 and it has since then evolved in a treatment option for chronic neuropathic pain [1].

2. Tonic SCS

The stimulation paradigm introduced by Shealy et al. is referred to as conventional or tonic stimulation. Tonic stimulation is applied with a frequency ranging from 40 to 80 Hz and a pulse width varying between 200 and 500 μs and at intensities which induce tingling sensations or paresthesias. Preclinically, stimulation intensity or amplitude is programmed at 66–90% of the intensity that generates regular muscle twitches in the animal. The concept of tonic SCS is based on the Gate Control Theory by Melzack and Wall [3]. The electrical pulses delivered by SCS activate Aβ fibers in the dorsal column which, via antidromic transmission, activate inhibitory interneurons in the spinal dorsal horn. These interneurons modulate incoming nociceptive input from Aδ and C fibers and release the inhibitory neurotransmitter γ-aminobutyric acid (GABA), thereby 'closing the gate.' The 'closed gate' prevents transmission of nociceptive signals to the brain and thereby inhibits pain sensation.

2.1. Spinal mechanisms of tonic SCS: role of GABA

Preclinical studies have established the involvement of the neurotransmitter GABA and the inhibitory GABAergic interneurons in the mechanism underlying tonic SCS mediated analgesia. Extracellular GABA concentrations in the dorsal horn of neuropathic rats were shown to be increased during SCS [4]. Furthermore, Janssen et al. showed reduced intracellular GABA immunoreactivity in the dorsal horn of rats with Partial Sciatic Nerve Ligation (PSNL) after 30 minutes of tonic SCS [5]. From this, it is concluded that tonic SCS induced GABA release into the extracellular space in the spinal dorsal horn and that this is a pivotal mechanism underlying the pain-relieving mechanism of tonic SCS. Intrathecal pharmacological studies have further elucidated and detailed the involvement of this GABAergic mechanism in tonic SCS, demonstrating in particular the $GABA_B$ receptor to be very important [6,7]. Importantly these preclinical findings have been translated into the clinic, demonstrating that the synergistic effect of administering a subclinical dose of the $GABA_B$ receptor agonist baclofen and tonic SCS turned SCS non-responders into responders [8].

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Presynaptic GABAergic inhibition regulated by BDNF contributes to neuropathic pain induction

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The gate control theory proposes the importance of both pre- and post-synaptic inhibition in processing pain signal in the spinal cord. However, although postsynaptic disinhibition caused by brain-derived neurotrophic factor (BDNF) has been proved as a crucial mechanism underlying neuropathic pain, the function of presynaptic inhibition in acute and neuropathic pain remains elusive. Here we show that a transient shift in the reversal potential (E_{GABA}) together with a decline in the conductance of presynaptic $GABA_A$ receptor result in a reduction of presynaptic inhibition after nerve injury. BDNF mimics, whereas blockade of BDNF signalling reverses, the alteration in $GABA_A$ receptor function and the neuropathic pain syndrome. Finally, genetic disruption of presynaptic inhibition leads to spontaneous development of behavioural hypersensitivity, which cannot be further sensitized by nerve lesions or BDNF. Our results reveal a novel effect of BDNF on presynaptic GABAergic inhibition after nerve injury and may represent new strategy for treating neuropathic pain.

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11.

Therapeutic Basis of Clinical Pain Modulation

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Abstract

Pain is a hallmark of almost all bodily ailments and can be modulated by agents, including analgesics and anesthetics that suppress pain signals in the central nervous system. Defects in the modulatory systems, including the endogenous pain-inhibitory pathways, are a major factor in the initiation and chronicity of pain. Thus, pain modulation is particularly applicable to the practice of medicine. This review summarizes the existing literature on pain modulation. Here, we critically reviewed the literature from PubMed on pain modulation published primarily within the past 5 years in high impact journals. Specifically, we have discussed important anatomical landmarks of pain modulation and outlined the endogenous networks and underlying mechanisms of clinically relevant pain modulatory methods. The Gate Control Theory is briefly presented with discussion on the capacity of pain modulation to cause both hyper- and hypoalgesia. An emphasis has been given to highlight key areas in pain research that, because of unanswered questions or therapeutic potential, merit additional scientific scrutiny. The information presented in this paper would be helpful in developing novel therapies, metrics, and interventions for improved patient management. Clin Trans Sci 2015; Volume 8: 848–856

Keywords: pain modulation, Gate Control Theory, opioids, inhibitory amino acids, cannabinoids, electroanalgesia, periaqueductal gray, rostral ventromedial medulla

Introduction

Pain modulation refers to the process by which the body alters a pain signal as it is transmitted along the pain pathway and explains, at least in part, why individual responses to the same painful stimulus sometimes differ. Modulation can also explain why the activation of pain neurons and the sensory experience of pain do not always coincide. Most importantly, pain modulation elucidates the mechanisms of action underlying clinical analgesia. In this paper, we have critically reviewed pain modulation literature by searching PubMed for primary research papers that elucidate therapeutically significant mechanisms in pain modulation. This review focuses on the following key questions: (i) does pain modulation have an analgesic effect, hyperalgesic effect, or both? (ii) What is the Gate Control Theory (GCT), and how does it impact our understanding of pain modulation? (ii) What are the clinically important pain modulation types? (iv) what are the outstanding questions in pain modulation research that could lead to new therapeutic approaches?

Does Pain Modulation Have an Analgesic Effect, Hyperalgesic Effect, or Both?

Opioids are widely recognized as the "gold standard" in pain control. Indeed, the use of opiates can cause hyperalgesia.[1] Watanabi[2] made a paradoxical observation: giving limited amounts of morphine to rats relieved the symptoms of pain; however, high doses of morphine led to pain-related responses in the rats. Interestingly, opioids can cause recipients to become hypersensitive to certain painful stimuli. While opioid-induced hyperalgesia is not the emphasis of this review, opiates offer a valuable example of pain modulation: they are capable of both increasing and decreasing the experience of pain. He et al.[3] showed that, in rats, inflammatory markers, particularly HMGB 1, contribute to neuropathic pain. These changes in pain sensation were implemented via modulatory pathways that could both increase and decrease the sensation of pain via the HMGB1 and HMGB1-RAGE pathways.[3] In a review of pain modulatory mechanisms, Heinricher et al.[4] concluded that descending modulation could be both "facilitatory" and "inhibitory." Additionally, these investigators noted that a single modulatory structure in the brain can often mediate both "facilitatory" and "inhibitory" modulation of pain.[4] Although, the term "modulation" is commonly assumed to have an exclusively analgesic connotation, pain modulation can lead to both analgesia and hyperalgesia.

Gate Control Theory

In a landmark paper, Wall and Melzack[5] proposed the GCT. While some details of the GCT have been shown to be incorrect or incomplete, it has proven to be a powerful tool for guiding pain research.[6–8] The GTC proposes that nociceptive and nonnociceptive signals are summated within the substantia gelatinosa (spinal cord).[6–8] If nociceptive signals outweigh nonnociceptive signals, a pain signal is propagated.[6,8] Wall and Melzack[5] also proposed that descending afferent fibers could modulate pain signals within the substantia gelatinosa. A visual representation of the pain circuit proposed by Wall and Melzack is shown in *Figure 1*.

The GCT broadly suggests that large nerves conduct nonnociceptive information and that smaller fibers conduct nociceptive information.[6,8] After the proposition of the theory, researchers tested it by electrically stimulating large fibers.[6] In a variety of studies, this type of stimulation has been found to provide pain relief.[6] Researchers continue to use the GTC rationale to propose new methods for achieving clinical pain relief. For example, Kessler and Hong invoked the GTC in explaining their investigation of whole body vibration as a potential therapy for diabetic neuropathy.[9] Similarly, Fournier and Elman[10] tested the use of pneumatic skin flattening as an analgesic technique. Their study emphasized its effect on pain transmission within the circuits described by the GTC.[10] Often, those who injure themselves instinctively rub the affected area. Within the context of the GCT, this natural response is unsurprising: the

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12.

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GABA Puts a Stop to Pain

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Abstract: A lack of inhibition, particularly that mediated by gamma-amino butyric acid (GABA), the main inhibitory transmitter of the central nervous system (CNS), is responsible for many pain states. Until recently, few GABA acting drugs were available and were prescribed mostly for relieving muscle spasms, anxiety and epilepsy, but rarely for pain. The basic metabolic pathway of GABA is well known and we are now beginning to understand the function of this neurotransmitter in the complex circuitry underlying pain, especially in the context of nerve injury. Analgesic compounds are now being developed targeting GABA transporters as well as GABA associated enzymes and receptors. Some GABA analogs act by inhibiting ion channels, a property that contributes to their analgesic effects. However, despite considerable progress in developing new compounds, the use of systemically acting GABAergic drugs is limited by unwanted side-effects on systems other than those involved in pain, and by the fact that in certain areas of the brain, GABA can enhance rather than reduce pain. The advent of new drugs targeting subtypes of GABA receptors and transporters and the possibility of using newly developed delivery systems, such as intrathecal pumps and viral vectors, to target specific areas of the nervous system will likely help circumvent these problems.

Keywords: Nociception, analgesia, hyperalgesia, peripheral nerve injury, GABA transporter, GABA receptor, glutamic acid decarboxylase, ion channel.

INTRODUCTION

While gamma-amino butyric acid (GABA) acting drugs have a long history for treating anxiety, new findings augur an increase in their use for treating pain. The cloning of the GABA receptor subunits, new anatomical, functional and behavioral studies on the effects of regional modulation of GABA receptors, development of new GABA receptor and transporter ligands and the emergence of gene therapy have opened many new possibilities.

GABA

GABA is found in almost every region of the brain and spinal cord but the understanding that GABA is an inhibitory neurotransmitter is relatively recent [1]. GABA is produced by the decarboxylation of glutamate; a reaction catalyzed by glutamic acid decarboxylase (GAD; Fig. **1**), and like the other classical neurotransmitters, is packaged into synaptic vesicles and released from axon terminals *via* Ca^{++} dependant exocytosis (Fig. **2**). Following its release, GABA is removed by either glial or presynaptic reuptake. In the cytoplasm, GABA transaminase converts GABA to succinic semialdehyde [2], which enters the Krebs cycle, leading to glutamate production. In glial cells there is an additional step in which glutamate is converted to glutamine before being returned to neurons where it is converted back to glutamate and then GABA (Fig. **2**).

GAD

There are two forms of GAD, GAD65 and GAD67, each coded by different genes [3,4]. GABAergic neurons in the CNS all contain both forms of GAD in different relative amounts with event related (phasic activity) firing pattern neurons expressing higher levels of GAD65 [5]. It is widely believed that GAD65 generates GABA released in synaptic vesicles while GAD67 generates cytoplasmic GABA which is either recycled without being released or is released extrasynaptically by reversed transport through a GABA transporter (see below) [3,6] (Fig. **3**). From this, one would conclude that GAD65 plays a greater role in GABAergic inhibition, as synaptic release of GABA is expected to be more effective than extrasynaptic release. This does not appear to be the case since the GAD67 enzyme is responsible for the production of most of the GABA found in the nervous system, and GAD65 mouse knockouts are essentially normal due to GAD67 mediated synaptic release [7]. In addition, the vast majority of axonal terminals in the spinal cord contain both forms of the enzyme [8] suggesting that synaptic release of GABA is not solely dependant on GAD65 i.e. 65. Of note, Linetska and colleagues [9] recently reported that an attenuated toxin, alpha-Latrotoxin, induces depletion of vesicular GABA followed by depletion of non-vesicular GABA, showing that it is possible to target the two compartments separately.

GATs

GABA transporters (GATs) carry GABA back into GABAergic neurons as well as astrocytes [10]. The transporters are divided into high (GAT1, GAT2 and GAT3) and low (BGT-1 (betaine GABA transporter)) affinity subgroups [11-18]. GAT activity is dependant on pyridoxal-phosphate (vitamin B6), which acts as a cofactor. Therefore, drugs that interfere with the binding of vitamin B6 will lead to a decrease in GAT activity and consequently increase GABA activity. Such drugs include a number of hydrazine

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GABA-A RECEPTOR ACTIVITY IN THE NORADRENERGIC LOCUS COERULEUS DRIVES TRIGEMINAL NEUROPATHIC PAIN IN THE RAT; CONTRIBUTION OF NAα1 RECEPTORS IN THE MEDIAL PREFRONTAL CORTEX

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Abstract—Trigeminal neuropathic pain is described as constant excruciating facial pain. The study goal was to investigate the role of nucleus locus coeruleus (LC) in a model of *chronic* orofacial neuropathic pain (CCI-ION). The study examines LC's relationship to both the medullary dorsal horn receiving trigeminal nerve sensory innervation and the medial prefrontal cortex. LC is a major source of CNS noradrenaline (NA) and a primary nucleus involved in pain modulation. Although descending inhibition of acute pain by LC is well established, contribution of the LC to facilitation of chronic neuropathic pain is also reported. In the present study, a rat orofacial pain model of trigeminal neuropathy was induced by chronic constrictive injury of the infraorbital nerve (CCI-ION). Orofacial neuropathic pain was indicated by development of whisker pad mechanical hypersensitivity. Hypersensitivity was alleviated by selective elimination of NA neurons, including LC (A6 cell group), with the neurotoxin anti-dopamine-β-hydroxylase saporin (anti-DβH-saporin) microinjected either intracerebroventricularly (i.c.v.) or into trigeminal spinal nucleus caudalis (spVc). The $GABA_A$ receptor antagonist, bicuculline, administered directly into LC (week 8) inhibited hypersensitivity. This indicates a valence shift in which increased $GABA_A$ signaling ongoing in LC after trigeminal nerve injury paradoxically produces excitatory facilitation of the *chronic* pain state. Microinjection of NAα1 receptor antagonist, benoxathian, into medial prefrontal cortex attenuated whisker pad hypersensitivity, while NAα2 receptor antagonist, idazoxan, was ineffective. Thus, $GABA_A$-mediated activation of NA neurons during CCI-ION can facilitate hypersensitivity through NAα1 receptors in the medial prefrontal cortex. These data indicate LC is a chronic pain generator. © 2016 Published by Elsevier Ltd on behalf of IBRO.

Key words: dopamine-beta-hydroxylase, anti-DβH-saporin, mechanical allodynia, spinal trigeminal caudalis, CCI-ION, chronic orofacial neuropathic pain.

INTRODUCTION

The pontine locus coeruleus (LC) nucleus is a major source of norepinephrine/noradrenaline (NA) in the central nervous system and a well-known mediator of descending inhibition of pain. The highly divergent efferent axonal projections of the LC innervate all levels of the neuraxis with an extensive network of ascending and descending projections to accentuate specific responses (Grzanna and Molliver, 1980; Westlund and Coulter, 1980; Westlund et al., 1981, 1982, 1983; Mantz et al., 1988; Aston-Jones et al., 2004; Gompf et al., 2010; Chandler and Waterhouse, 2012; Eschenko et al., 2012). A major NA efferent pathway from the LC innervates the medial prefrontal cortex. This circuit optimizes behaviorally relevant, cognitive functions (Aston-Jones and Cohen, 2005; Marzo et al., 2014). For example, salient internal or external events can alter function or "reset" large-scale neural populations. This can be mediated by the targeted release of NA in the medial prefrontal cortex and can then shift the excitatory/inhibitory balance of the medial prefrontal cortex to a more excitable state. Therefore, we hypothesized that continuous activation within the NA LC-medial prefrontal cortex circuit provided by a chronic nerve injury model could shift pain modulation from inhibition to facilitation. To test this, we evaluated neuropathic pain behavior after either: (1) destruction of NA neurons in the LC; or (2) administration of α-adrenergic antagonists into the medial prefrontal cortex. Elimination of ascending and descending NA input was tested, as was the effect of NAα1 and NAα2 receptor activation.

Modulation of nociceptive transmission and pain perception are influenced by direct NA projections to trigeminal and spinal cord dorsal horn neurons. Several studies have shown that neurons of both the LC and the rostral ventromedial nucleus raphe magnus can either

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Abbreviations: ATF3, activating transcription factor 3; BEN, benoxathian hydrochloride; BIC, bicuculline methiodide; CCI-ION, chronic constriction injury of trigeminal nerve maxillary V2 infraorbital branch; DβH, dopamine-β-hydroxylase; $GABA_A$, gamma amino butyric acid receptor A; GAD65, glutamate decarboxylase; i.c.v., intracerebroventricularly; IDA, idazoxan hydrochloride; LC, nucleus locus coeruleus; mPFC, medial prefrontal cortex; NA, noradrenaline; NAα1 or NAα2, noradrenergic receptor alpha 1 or noradrenergic receptor alpha 2; spVc, spinal trigeminal nucleus caudalis; TG, trigeminal ganglion; VEH, vehicle; Vth, trigeminal nerve.

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Chapter 11
Targeting the $GABA_B$ Receptor for the Treatment of Pain

Sam J. Enna and Kenneth E. McCarson

Abstract Pharmacological and neurobiological data indicate that γ-aminobutyric acid (GABA) is involved in pain processing and perception, with both basic and clinical studies demonstrating that selective activation of GABAergic transmission yields a nociceptive response. This is particularly true for agents that stimulate $GABA_B$ receptors. While these findings are in accord with the neuroanatomical localization of $GABA_B$ receptors on nociceptive pathways, such work has yet to yield a clinically useful analgesic. Some reasons for this failure are the side effects associated with $GABA_B$ agonists and the tolerance that develops to their therapeutic effects. Described in this chapter are the neuroanatomical localization and function of GABAergic neurons as they relate to nociception and to the antinociceptive responses to $GABA_B$ receptor agonists. Particular emphasis is placed on detailing possible reasons why GABAergic compounds, especially orthosteric receptor agonists, display limited clinical efficacy as analgesics. Among these are the variations in GABA receptor expression and function that occur with the persistent receptor activation associated with a painful stimulus and the chronic administration of orthosteric compounds. Strategies are described for developing GABAergic drugs, such as allosteric $GABA_B$ receptor modulators, that by selectively activating sites associated with pain pathways provoke fewer side effects and less tolerance than orthosteric agents.

Keywords $GABA_B$ receptors • Nociception • Neuropathic pain • $GABA_B$ pharmacology

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OROFACIAL PAIN – DIAGNOSTIC AND THERAPEUTIC CHALLENGES

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SUMMARY – The concept of diagnostics and therapy of musculoskeletal and neuropathic diseases of the stomatognathic system, which are the subject of this paper, has been developing for decades. It can be said that in order to avoid misunderstanding, the orofacial pain as a clinical problem, in the narrower sense, involves non-odontogenic and non-malignant causes of orofacial region. In this study, the results of clinical diagnosis of the population of 557 consecutive patients with orofacial pain based on multidisciplinary diagnostics were evaluated. 15.6% of patients have given up on the participation in the study. It has been shown that the patients who dropped out of the study were significantly older (p=0.0411) than those who agreed to participate, but there was no difference in gender ratio (p=0.185) since the proportion of female patients prevailed. In an analysis of 84.4% of patients participating in the study, the elevated anxiety values were established (mean value on STAI 1 was 39.2 and STAI 2 was 41.1) and statistical significance was found in correlation between elevated anxiety and intensity of pain as shown on visual analogue scale on open mouth (p<0.0001). Compared to the age, the statistical significance was for STAI 1 (p=0.0097) but not for STAI 2 (p=0.5599). The most common form of therapy is Michigan stabilization splint: for disc displacement of temporomandibular joint (TMJ) in 38.9% of patients and in combination with physiotherapy in 18.7% of patients; for osteoarthritis of TMJ in 28.4% and in combination with physiotherapy in 26.4% of patients. The treatment with anticonvulsant drugs for trigeminal neuralgia predominates in 54.3% of patients, which is combined with acupuncture in 25.7% of patients and only acupuncture in 17.1% of patients. In this study, a multidisciplinary co-operation in initial diagnostics and differential was designed to develop subspecialist knowledge on orofacial pain.

Key words: *orofacial pain, temporomandibular joint, anxiety, trigeminal neuralgia*

Introduction

Generally, the pathology of orofacial pain is most commonly caused by the disease of the teeth (odontogenic pain), which is a domain of dental medicine and it should not be a diagnostic-therapeutic challenge in itself. Apart from dental caries and periodontal diseases, musculoskeletal and neuropathological diseases are the most common cause of orofacial pain[1,2]. The relationship between the proprioceptive pattern of joint functioning and muscle pain-forming functioning is best described by the term encompassing a common name of myoarthropathy of the masticatory sys-

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Pain Part 5b: Non-Odontogenic Dysfunctional Pain

Abstract: Orofacial chronic pain provides a significant challenge to all clinicians and the patients seeking treatment for it. Due to the anatomical and regional complexities, diagnosis can be extremely difficult, and due to the lack of cross specialty training, patients will undergo a variety of treatment under different disciplines. Dysfunctional pain provides a unique challenge for patient management and requires a multidisciplinary team.

Clinical Relevance: Lack of recognition of dysfunctional chronic pain can result in inappropriate dental treatment and further damage. to the patient. Appropriate patient reassurance and referral to an orofacial pain multidisciplinary team is recommended as most of these conditions require medical management.

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Persistent post-surgical pain without demonstrable neuropathy

This is defined as pain that is present one year or longer post-surgical procedure, that is unexplained by local factors and is best described as neuropathic in nature.

Non-odontogenic dysfunctional pain is often difficult to diagnose because it is poorly understood.[1] Even defining and categorizing such persistent pain is challenging. Non-odontogenic pain may represent half of all cases of persistent tooth pain, as shown by a recent systematic review of prospective studies that reported the frequency of non-odontogenic pain in patients who had undergone endodontic procedures. Non-odontogenic pain was defined as dento-alveolar pain present for 6 months or more after endodontic treatment without evidence of dental pathology. Endodontic procedures reviewed were non-surgical root canal treatment, retreatment, and surgical root canal treatment: 770 articles were retrieved and reviewed, 10 met the inclusion criteria with a total of 3,343 teeth enrolled within the included studies; 1,125 had follow-up information regarding pain status. The authors identified non-odontogenic pain in 3.4% (95% confidence interval, 1.4–5.5% frequency of occurrence).[2]

The prevalence of persistent post-surgical pain in the trigeminal system may be low compared with other surgical sites. However, a recent report highlights the importance of dentists' awareness of neuropathic pain (NePain) before trying to solve apparent 'toothache' with conventional dental treatment, which will not be effective and results in additional harm to the patient.[3]

However, when one considers the significant frequency of dental surgical procedures undertaken, then significant numbers of individuals should be affected by both post-traumatic neuropathy and persistent post-surgical pain but, fortunately, the condition remains rarely associated with dentistry. This may be because most procedures are performed under local anaesthetic, which helps prevent central sensitization.

Risk factors for developing persistent post-surgical pain include:

- Genetics (deficiency of the enzyme catecholamine-O-methyltransferase);
- Preceding pain (intensity and chronicity);
- Psychosocial factors (ie fear, memories, work, physical levels of activity, somatization);
- Age (older = increased risk);
- Gender (female = increased risk); and
- The surgical procedure and technique (tension due to retraction).[4]

All these persistent post-surgical pain conditions may be attributable to post-traumatic neuropathy but it is difficult to be conclusive without a demonstrable neuropathic area in relation to the previous surgery.

Idiopathic or dysfunctional chronic pain

This group includes persistent

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REVIEW ARTICLE Open Access

Multi-dimensionality of chronic pain of the oral cavity and face

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Abstract

Orofacial pain in its broadest definition can affect up to 7% of the population. Its diagnosis and initial management falls between dentists and doctors and in the secondary care sector among pain physicians, headache neurologists and oral physicians. Chronic facial pain is a long term condition and like all other chronic pain is associated with numerous co-morbidities and treatment outcomes are often related to the presenting co-morbidities such as depression, anxiety, catastrophising and presence of other chronic pain which must be addressed as part of management . The majority of orofacial pain is continuous so a history of episodic pain narrows down the differentials. There are specific oral conditions that rarely present extra orally such as atypical odontalgia and burning mouth syndrome whereas others will present in both areas. Musculoskeletal pain related to the muscles of mastication is very common and may also be associated with disc problems. Trigeminal neuralgia and the rarer glossopharyngeal neuralgia are specific diagnosis with defined care pathways. Other trigeminal neuropathic pain which can be associated with neuropathy is caused most frequently by trauma but secondary causes such as malignancy, infection and auto-immune causes need to be considered. Management is along the lines of other neuropathic pain using accepted pharmacotherapy with psychological support. If no other diagnostic criteria are fulfilled than a diagnosis of chronic or persistent idiopathic facial pain is made and often a combination of antidepressants and cognitive behaviour therapy is effective. Facial pain patients should be managed by a multidisciplinary team.

Keywords: Facial pain, Temporomandibular disorders, Trigeminal neuralgia, Burning mouth syndrome, Neuropathic pain, Persistent idiopathic facial pain, Cognitive behaviour therapy, Biopsychosocial

Introduction

This review will look at pain that predominantly presents in the lower part of the face and the mouth. The epidemiology and classification will be discussed and the diagnostic criteria presented together with a brief mention of management. The review will include a discussion about the multidimensionality of facial pain as there is increasing evidence throughout the field of chronic pain that psychosocial factors impact significantly not just on outcomes from management but also act as prognosticators and can even affect the way symptoms are reported. Many patients will have more than one pain diagnosis and there may also be an underlying psychiatric or personality disorder which pre disposes to chronic pain and which will alter the presentation and significantly affect management [1].

When problems arise in this area patients become very confused as they are unsure as to whether they should consult a doctor or dentist. Equally health care professionals often struggle as it is rare for medical students to be taught in depth about the mouth and surrounding structures. On the other hand dentists do not have in depth knowledge of the biopsychosocial approach to head and neck pain, remain confused about management of non-dental pain and are very restricted in the types of drugs that they can prescribe [2,3]. Hence as Hals et al. [4] point out these patients often get stigmatized as "difficult" as few health care professionals feel capable of helping them single handed as they really need a multi-professional team. A recent study of the healthcare "journey" of chronic orofacial pain patients in the UK showed that 101 patients had attended a mean

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ACCOMMODATION TO DIAGNOSIS OF TRIGEMINAL NEURALGIA

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SUMMARY – Trigeminal neuralgia is one of the most common causes of facial pain. It implies short lasting episodes of unilateral electric shock-like pain with abrupt onset and termination, in the distribution of one or more divisions of the trigeminal nerve that are triggered by innocuous stimuli. Most cases of trigeminal neuralgia are caused by compression of the trigeminal nerve root. Depending on the etiology, trigeminal neuralgia can be classified as classic trigeminal neuralgia or painful trigeminal neuropathy. It may be precipitated by some actions at trigger zones. The diagnosis of trigeminal neuralgia is based on diagnostic criteria for classic trigeminal neuralgia, neuroimaging and electrophysiologic trigeminal reflex testing. Treatment of classic trigeminal neuralgia for most patients is pharmacological therapy, while surgical approach is reserved for patients that are refractory to medical therapy and in cases of painful trigeminal neuropathy.

Key words: *Trigeminal neuralgia – therapy; Trigemnial neuralgia – surgery; Central nervous system – vascular malformations; Blinking; Carbamazepine*

Introduction

Trigeminal neuralgia (TN) is one of the most common causes of facial pain, with the annual incidence of 4 to 13 *per* 100 000 people and increasing gradually with age[1,2]. It is one of the most frequent neuralgias in the elderly population, with the male to female ratio 1:1.7[3]. Trigeminal nerve starts at the midlateral surface of the pons, and its sensory ganglion (gasserian ganglion) resides in Meckel's cave in the floor of the middle cranial fossa. It brings sensory supply to the face and the sensory and motor supply to the muscles of mastication. It divides into three main branches, ophthalmic, maxillary and mandibular. TN is characterized by recurrent short lasting episodes of unilateral electric shock-like pain with abrupt onset and termination, in the distribution of one or more divisions of the trigeminal nerve that are triggered by innocuous stimuli[4].

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Most TN cases are caused by compression of the trigeminal nerve root, usually within a few millimeters of entry into the pons[5]. Compression can be caused by an aberrant loop of an artery or vein (80 to 90 percent of cases)[5-7], or vestibular schwannoma (acoustic neuroma), meningeoma, epidermoid or other cyst, or rarely a saccular aneurysm or arteriovenous malformation[8-14]. Idiopathic TN or TN caused by vascular compression is considered classic TN, and other causes of TN *via* compression are classified as painful trigeminal neuropathy. The mechanism by which compression of the nerve leads to symptoms appears to be related to demyelination in a circumscribed area around the compression[15,16]. The mechanism by which demyelination results in the symptoms of TN is not entirely clear. It is also possible that there is a role of the central pain mechanisms. Demyelination of one or more of the trigeminal nerve nuclei may also be caused by multiple sclerosis or other structural lesions of the brainstem, although vascular compression has also been noted in these patients[17].

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Neuropathic orofacial pain – diagnostic and therapeutic challenges

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Key words: neuropathic orofacial pain- diagnostic; neuropathic orofacial pain- therapy

Abbreviations:

CNS	– Central nervous system
DN4	– Neuropathic Pain Diagnostic Questionnaire
EFIC	– The European Pain Federation
IHS	– The International Headache Society
IASP	– The International Association for the Study of Pain
ICHD-3	– 3rd International Classification of Headache Disorders
LANSS	– The Leeds Assessment of Neuropathic Symptoms and Signs
NPQ	– Neuropathic Pain Questionnaire
NSAIDs	– non-steroidal anti-inflammatory drugs
OFP	– Chronic neuropathic orofacial pain
PHN	– postherpetic neuralgia
SSNRIs	– selective serotonin norepinephrine reuptake inhibitors
SSRIs	– selective serotonin reuptake inhibitors
TAD	– tricyclic antidepressants
TN	– trigeminal neuralgia

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Abstract

Chronic neuropathic orofacial pain (OFP) is the leading symptom for a wide range of conditions. It can exist independently of any addition signs, symptoms and radiological or laboratory abnormalities. In addition to physical suffering, OFP causes emotional, psychological and social disturbances and thus significantly influences the quality of life of those affected. Several key factors make OFP a complex diagnostic and therapeutic challenge. These include a lack of diagnostic criteria that are both validated and readily applicable in clinical settings and a lack of sufficient education about pain in undergraduate medical training programs. There is also a need to develop more analgesic therapies offering improved efficacy and side effect profiles. Finally, the provision of analgesic therapies by health insurance programs need to be harmonized with the most current evidence-based treatment protocols. In addition to offering recommendations in these areas, this paper provides an overview of the most common clinical forms of nonodontogenic OFP, epidemiological data, and current diagnostic and therapeutic options.

INTRODUCTION

Pain is one of the most unpleasant aspects of many diseases. To underscore the importance of pain as a global health problem, the International Association for the Study of Pain (IASP) launched its first "Global Year Against Pain," in 2004 with the slogan; *Pain management should be a human right*. Each IASP annual campaign is dedicated to the study of pain arising from particular conditions or etiologies. For example, 2013 marked the year against chronic pain, whereas orofacial pain was the focus in 2014, which was followed by a year against neuropathic pain in 2015 *(1)*. Such campaigns help raise awareness for the many ways in which various types of pain effect health, ranging from a vital warning sign to a debilitating condition. Acute pain, which signals the occurrence of injury or disease, provides an important protective function. Conversely, chronic pain provides no real or potential benefits, resulting only in unnecessary suffering. This is particularly true of neuropathic pain, an important component of numerous medical conditions *(2)*. Whatever its origin, pain is recognized globally as one of the primary reasons for seeking medical attention. The pain suffered by individuals creates not only personal but also societal costs. Communities are burdened with both the direct costs of healthcare utilization and the indirect costs of reduced worker productivity and increased absenteeism due to pain.

One of the most significant sources of pain in the human body is the orofacial region, a highly sensitive area with abundant pain receptors (3).

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LETTERS

Reversal of pathological pain through specific spinal $GABA_A$ receptor subtypes

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Inflammatory diseases and neuropathic insults are frequently accompanied by severe and debilitating pain, which can become chronic and often unresponsive to conventional analgesic treatment[1,2]. A loss of synaptic inhibition in the spinal dorsal horn is considered to contribute significantly to this pain pathology[3–7]. Facilitation of spinal γ-aminobutyric acid (GABA)ergic neurotransmission through modulation of $GABA_A$ receptors should be able to compensate for this loss[8,9]. With the use of $GABA_A$-receptor point-mutated knock-in mice in which specific $GABA_A$ receptor subtypes have been selectively rendered insensitive to benzodiazepine-site ligands[10–12], we show here that pronounced analgesia can be achieved by specifically targeting spinal $GABA_A$ receptors containing the α2 and/or α3 subunits. We show that their selective activation by the non-sedative ('α1-sparing') benzodiazepine-site ligand L-838,417 (ref. 13) is highly effective against inflammatory and neuropathic pain yet devoid of unwanted sedation, motor impairment and tolerance development. L-838,417 not only diminished the nociceptive input to the brain but also reduced the activity of brain areas related to the associative-emotional components of pain, as shown by functional magnetic resonance imaging in rats. These results provide a rational basis for the development of subtype-selective GABAergic drugs for the treatment of chronic pain, which is often refractory to classical analgesics.

More than 40 years ago, the gate control theory of pain[14] proposed that inhibitory neurons in the superficial dorsal horn of the spinal cord control the relay of nociceptive signals (that is, those evoked by painful stimuli) from the periphery to higher areas of the central nervous system. The pivotal role of inhibitory GABAergic and glycinergic neurons in this process has recently been demonstrated in several reports indicating that a loss of inhibitory neurotransmission underlies several forms of chronic pain[3–7]. Despite this knowledge, inhibitory neurotransmitter receptors have rarely been considered as targets for analgesic treatment. In fact, classical benzodiazepines, which are routinely used for their sedative, anxiolytic and anticonvulsant activity, largely lack clear analgesic efficacy in humans when given systemically[15]. To address this obvious discrepancy we investigated the molecular basis of GABAergic pain control in the spinal cord in an integrative approach based on an electrophysiological and behavioural analysis of genetically modified mice and on functional imaging in rats.

We first tested whether benzodiazepines exert antinociceptive effects at the level of the spinal cord by employing the mouse formalin assay, a model of tonic chemically induced pain. When the classical benzodiazepine diazepam was injected intrathecally into the lumbar spinal canal at doses of 0.01–0.09 mg per kg body weight, an apparent dose-dependent and reversible antinociception was obtained that could be antagonized by systemic treatment with the benzodiazepine antagonist flumazenil (10 mg kg^{-1} intraperitoneally (i.p.)) (Supplementary Fig. 1).

We next sought to identify the $GABA_A$ receptor isoforms responsible for this antinociception. $GABA_A$ receptors are heteropentameric ion channels composed from a repertoire of up to 19 subunits[16]. Benzodiazepine-sensitive isoforms are characterized by the presence of the γ2 subunit and one of four α subunits (α1, α2, α3 or α5)[17]. The generation of four lines of $GABA_A$-receptor point-mutated knock-in mice (α1(H101R), α2(H101R), α3(H126R) and α5(H105R)), in which a conserved histidine residue had been mutated to arginine, rendering the respective subunit insensitive to diazepam, has enabled the attribution of the different actions of diazepam to the individual $GABA_A$ receptor isoforms[10–12]. It also became possible to attribute the sedative effects of diazepam to $GABA_A$ receptors containing an α1 subunit[10] and the anxiolytic effect to those containing an α2 subunit[11] or—at high receptor occupancy—an α3 subunit[18]. We then compared the antinociceptive efficacy of intrathecal diazepam (0.09 mg kg^{-1}) in wild-type mice with that obtained in the four types of $GABA_A$-receptor point-mutated mice in models of inflammatory hyperalgesia induced by subcutaneous injection of zymosan A into one hindpaw and of neuropathic pain evoked by chronic constriction of the left sciatic nerve (chronic constriction injury (CCI) model).

Wild-type mice and all four types of mutant mice developed nearly identical pain sensitization after induction of inflammation or peripheral nerve injury (Fig. 1a, c). In wild-type mice, intrathecal diazepam (0.09 mg kg^{-1}) reversibly reduced inflammatory heat hyperalgesia (Fig. 1b), as well as CCI-induced heat hyperalgesia (Fig. 1d), cold allodynia (Fig. 1e) and mechanical sensitization (Fig. 1f) by 82 ± 13%, 92 ± 6% and 79 ± 9% (means ± s.e.m.), respectively. Responses of the non-inflamed or uninjured side were not significantly changed (Fig. 1a, c), indicating that spinal diazepam acted as an anti-hyperalgesic agent rather than as a general analgesic. Almost identical anti-hyperalgesic effects to those in wild-type mice were seen in mice carrying diazepam-insensitive α1 subunits. By contrast, α2(H101R) mice showed a pronounced reduction in diazepam-induced anti-hyperalgesia, which was consistently observed in all pain models tested. α3(H126R) and α5(H105R) mice showed smaller reductions, which occurred only in a subset of models. Importantly, intrathecal diazepam did not change spontaneous motor activity (Fig. 1g), indicating that the action of diazepam

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REVIEW ARTICLE

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The Pharmacology and Mechanisms of Action of New Generation, Non-Benzodiazepine Hypnotic Agents

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Abstract

The new generation hypnotic drugs, zolpidem, zopiclone and zaleplon, are at least as efficacious in the clinic as benzodiazepines and may offer advantages in terms of safety. These drugs act through the BZ binding sites associated with $GABA_A$ receptors, but show some differences from benzodiazepines in pharmacological effects and mechanisms of action. Of particular interest is the finding that zolpidem shows a wide separation between doses producing sedative effects and those giving rise to other behavioural actions, and induces less tolerance and dependence than benzodiazepines. Zolpidem also demonstrates selectivity for $GABA_A$ receptors containing α_1 subunits. Recent studies using genetically modified mice have confirmed that receptors containing $alpha_1$ subunits play a particularly important role in mediating sedative activity, thus providing an explanation for the pharmacological profile of zolpidem.

1. Introduction

When benzodiazepines were introduced, some four decades ago, as a treatment for insomnia, they represented a major advance in the therapy of this disorder. Benzodiazepines are effective hypnotic agents and are much safer than drugs used previously, such as barbiturates. However, benzodiazepines are not devoid of undesirable effects, and chronic treatment can lead to tolerance and dependence. Considerable efforts have consequently been expended in the search for non-benzodiazepine hypnotic drugs that have more selective profiles and fewer side effects, while acting through similar neural mechanisms to benzodiazepines. Three such drugs, zolpidem, zopiclone and zaleplon, have been developed and introduced into medical practice in recent years.

2. Pharmacology of New Generation Hypnotic Drugs

It is interesting to note that the search for new hypnotic drugs, which are as effective as benzodiazepines but with a better safety profile, was focused on drugs that had similar mechanisms of action to the benzodiazepines, showing affinity for the so-called benzodiazepine or BZ receptor. The three new generation hypnotic drugs that have reached the market so far, zolpidem, zopiclone and zaleplon, all promote sleep by enhancing the activity of the inhibitory neurotransmitter, GABA, at its receptors in the brain, but laboratory research indicates clear differences in their pharmacological profiles and mechanisms of action.[1–3] Their clinical profiles are also quite distinct.

Zopiclone is a drug with a short or intermediate

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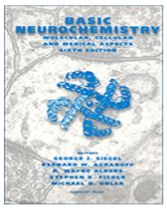

Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 6th edition.

GABA Receptor Physiology and Pharmacology

Richard W Olsen and Timothy M DeLorey.

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GABA receptors have been identified electrophysiologically and pharmacologically in all regions of the brain

Go to:

Because GABA is widely distributed and utilized throughout the CNS, early GABAergic drugs had very generalized effects on CNS function. The development of more selective agents has led to the identification of at least two distinct classes of GABA receptor, $GABA_A$ and $GABA_B$. They differ in their pharmacological, electrophysiological and biochemical properties. Electrophysiological studies of the $GABA_A$-receptor complex indicate that it mediates an increase in membrane conductance with an equilibrium potential near the resting level of −70 mV. This conductance increase often is accompanied by a membrane hyperpolarization, resulting in an increase in the firing threshold and, consequently, a reduction in the probability of action potential initiation, causing neuronal

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Benzodiazepine dependence and its treatment with low dose flumazenil

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Globally benzodiazepines remain one of the most prescribed medication groups, especially in the primary care setting. With such high levels of prescribing it is not surprising that benzodiazepine dependence is common, cutting across all socioeconomic levels. Despite recognition of the potential for the development of iatrogenic dependence and the lack of any effective treatment, benzodiazepines continue to be widely prescribed in general practice. Conventional dependence management, benzodiazepine tapering, is commonly a protracted process over several weeks or months. It is often associated with significant withdrawal symptoms and craving leading to patient drop out and return to use. Accordingly, there is a worldwide need to find effective pharmacotherapeutic interventions for benzodiazepine dependence. One drug of increasing interest is the $GABA_A$ benzodiazepine receptor antagonist/partial agonist, flumazenil. Multiple bolus intravenous infusions of low dose flumazenil used either with or without benzodiazepine tapering can reduce withdrawal sequelae, and/or longer term symptoms in the months following withdrawal. Preliminary data suggest that continuous intravenous or subcutaneous flumazenil infusion for 4 days significantly reduces acute benzodiazepine withdrawal sequelae. The subcutaneous infusion was shown to be tissue compatible so the development of a longer acting (i.e. several weeks) depot flumazenil formulation has been explored. This could be capable of managing both acute and longer term benzodiazepine withdrawal sequelae. Preliminary *in vitro* water bath and *in vivo* biocompatibility data in sheep show that such an implant is feasible and so is likely to be used in clinical trials in the near future.

Introduction

In 1959 the clinical introduction of the first benzodiazepine, chlordiazepoxide (Librium), promoted as a safe tranquillizer heralded a new era in the 'control of personal and emotional problems' and was a landmark of modern psychopharmacology. In the space of a few short years and accompanied by sophisticated promotional campaigns many other benzodiazepines were developed and released, with diazepam (Valium) the best known, being marketed in 1963. By the 1970s and early 1980s benzodiazepines had become the most commonly prescribed class of drug in the world. Soon after their introduction, however, reports of benzodiazepine dependency emerged [1]. Initial reports of dependency were subsequently supported by studies in animals [2] and humans [3, 4]. Despite concerns about possible long term adverse effects of benzodiazepine use, and calls for research into these effects stemming from as early as 1980 [5], benzodiazepines remain one of the most widely prescribed class of drugs in the world. While many countries now have guidelines recommending short term use with minimum doses, these are frequently ignored with long term prescribing of benzodiazepines actually rising in certain socioeconomic groups, notably the elderly and those on concessionary benefits [5].

Benzodiazepine mode of action

Benzodiazepines enhance the effects of γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the

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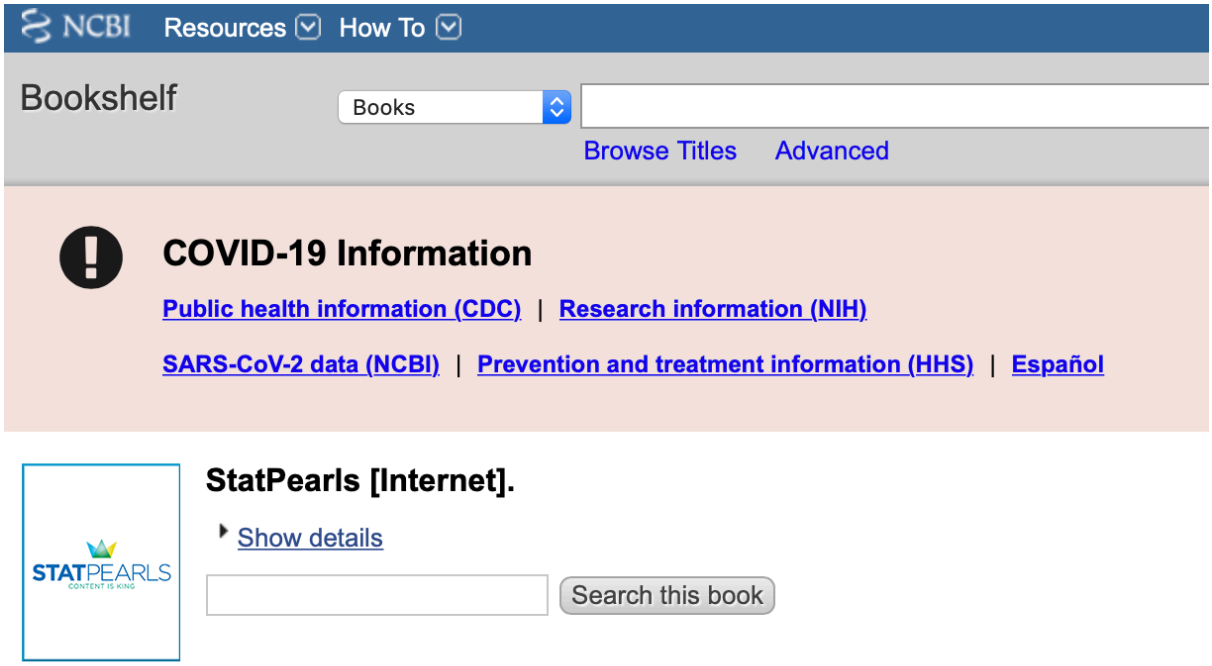

Neuroanatomy, Cranial Nerve 5 (Trigeminal)

Trevor Huff; Daniel T. Daly.

Author Information

Last Update: November 19, 2020.

Introduction

Go to:

The trigeminal nerve is the fifth cranial nerve (CN V). Its primary function is to provide sensory and motor innervation to the face. The trigeminal nerve consists of three branches on either side that extend to different territories of the face. These branches join at the trigeminal ganglia which are located within the Meckel cave of the cranial cavity. The different branches are namely the ophthalmic (V1), maxillary (V2), and mandibular (V3) nerves. The ophthalmic nerve is responsible for sensory innervation of the face and skull above the palpebral fissure as well as the eye and portions of the nasal cavity. The maxillary nerve is also a sensory branch and innervates portions of the nasal cavity, sinuses, maxillary teeth, palate, and the middle portion of the face and skull above the mouth and below the forehead. The mandibular nerve is unique in that it contains both sensory and motor fibers. It provides sensory innervation of the buccal mucosa, mandibular teeth, and the skin below

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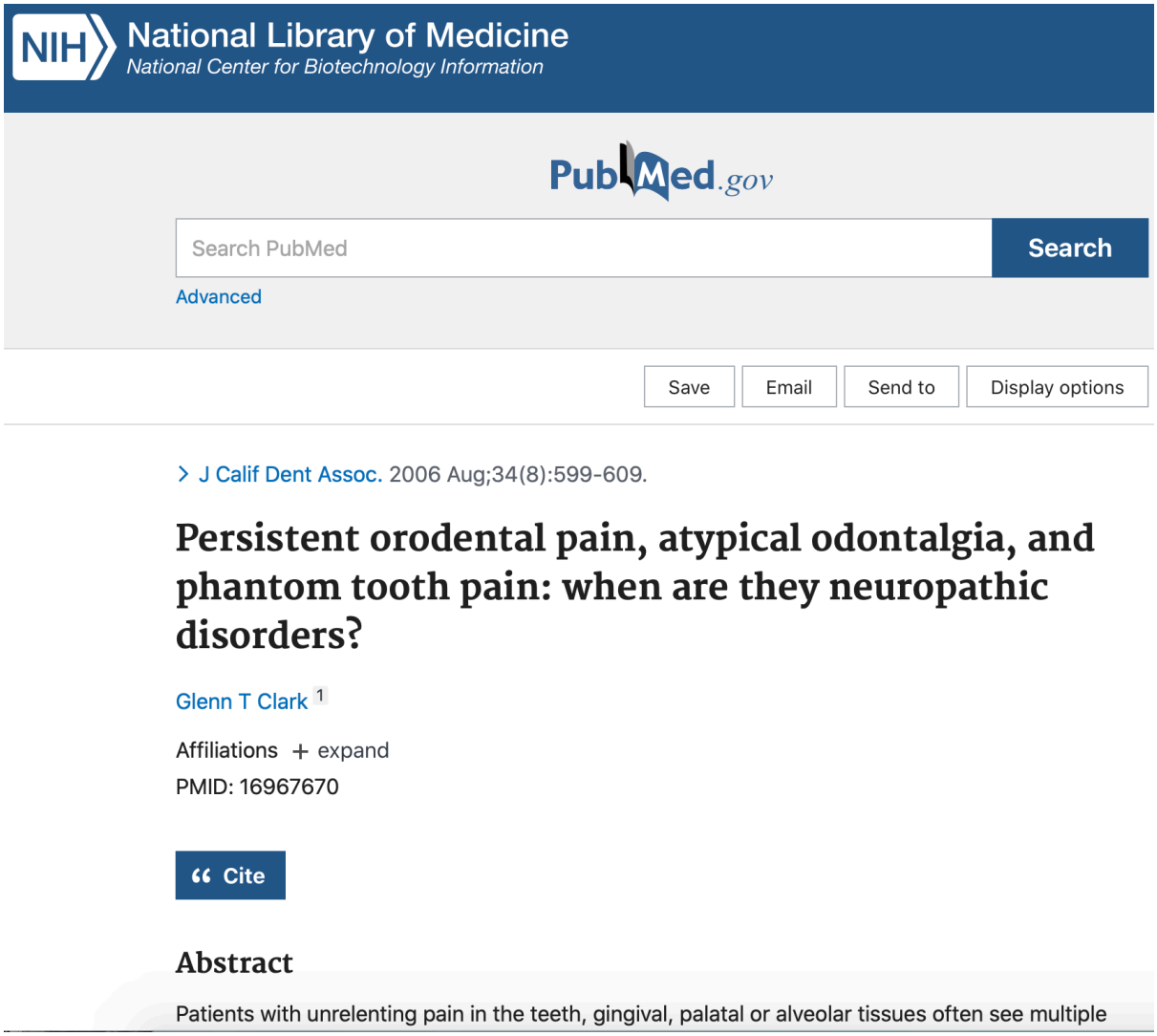
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J Calif Dent Assoc. 2006 Aug;34(8):599-609.
Persistent orodental pain, atypical odontalgia, and phantom tooth pain: when are they neuropathic disorders?
Glenn T Clark 1
Affiliations + expand
PMID: 16967670
Cite
Abstract
Patients with unrelenting pain in the teeth, gingival, palatal or alveolar tissues often see multiple

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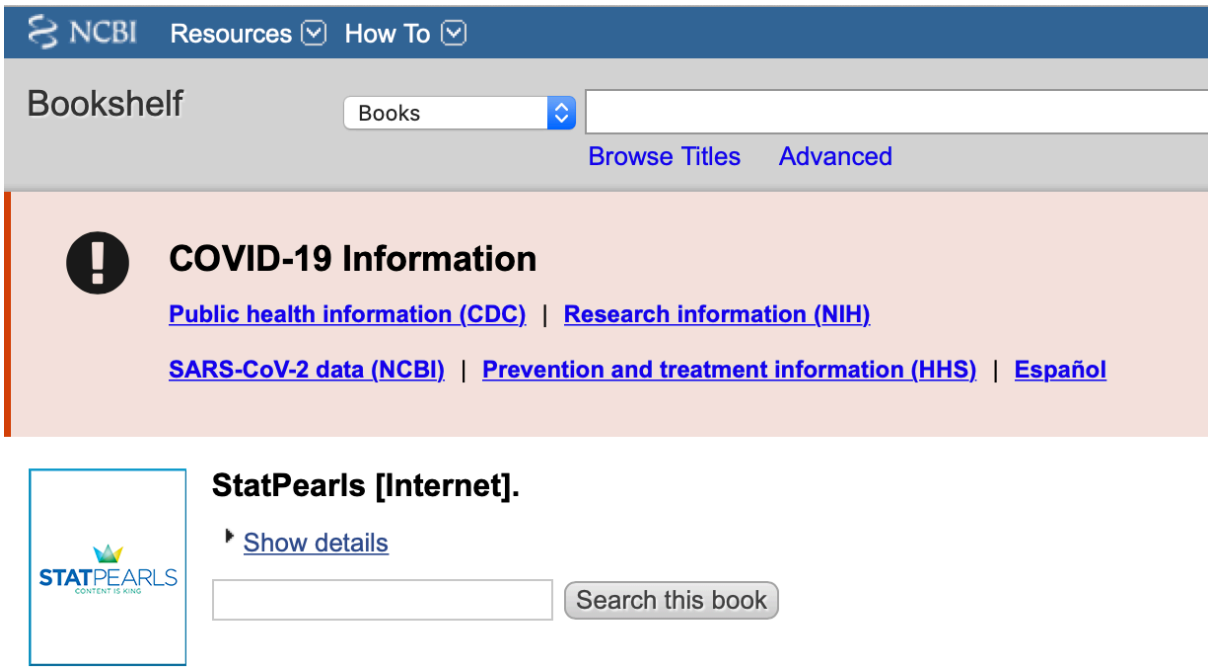

Barbiturate Toxicity

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Author Information

Last Update: July 2, 2020.

Continuing Education Activity

Go to:

Barbiturates are a class of sedative-hypnotic drugs. They are commonly used as antiepileptics (phenobarbital) and for the induction of general anesthesia (thiopental). This activity illustrates the evaluation and management of barbiturate toxicity and reviews the role of the interprofessional team in improving care for patients with this condition.

Objectives:

- Describe the epidemiology of barbiturate toxicity.
- Review the symptoms of withdrawal in the physical examination of patients with barbiturate toxicity.
- Explain the use of immunoassays (EIA) in the detection of the drug in patients with

28.

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Historical Review for British Journal of Pharmacology

Advantages of an Antagonist: Bicuculline and Other GABA Antagonists

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Abstract

The convulsant alkaloid bicuculline continues to be investigated more than 40 years after the first publication of its action as an antagonist of receptors for the inhibitory neurotransmitter GABA. This historical perspective highlights key aspects of the discovery of bicuculline as a GABA antagonist and the sustained interest in this and other GABA antagonists. The exciting advances in the molecular biology, pharmacology and physiology of GABA receptors provide a continuing stimulus for the discovery of new antagonists with increasing selectivity for the myriad of GABA receptor subclasses. Interesting GABA antagonists not structurally related to bicuculline include gabazine, salicylidene salicylhydrazide, RU5135 and 4-(3-biphenyl-5-(4-piperidyl)-3-isoxazole. Bicuculline became the benchmark antagonist for what became known as $GABA_A$ receptors, but not all ionotropic GABA receptors are susceptible to bicuculline. In addition, not all $GABA_A$ receptor antagonists are convulsants. Thus there are still surprises in store as the study of GABA receptors evolves.

Key words

GABA receptors, Antagonists, Bicuculline, Gabazine, Picrotoxin

Running head: Bicuculline and other GABA antagonists

Abbreviations
GABA, γ-aminobutyric acid; gabazine, SR 95531, 4-[6-imino-3-(4-methoxyphenyl)pyridazin-1-yl] butanoic acid; RU5135, 3α-hydroxy-16-imino-17-aza-5β-androstan-11-one; 4-PIOL, 5-(4-piperidyl)-3-isoxazolol

5843 words, 5 figures

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Effect of 2-hydroxy-saclofen, an antagonist of $GABA_B$ action, upon the binding of baclofen and other receptor ligands in rat cerebrum

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(Accepted 15 May 1990)

Key words: γ-Aminobutyric acid-B antagonist; Inhibitory postsynaptic potential; γ-Aminobutyric acid-B receptor; Phaclofen

2-Hydroxysaclofen (2-OH-saclofen), a newly available compound which blocks certain physiological actions of the γ-aminobutyric $acid_B$ ($GABA_B$) agonist, baclofen, was found to displace [^{3}H]baclofen at least 10-fold more potently than did phaclofen, a previously available antagonist of $GABA_B$ action. 2-OH-Saclofen reduced both the affinity and apparent density of baclofen binding sites and displaced baclofen binding at least 60-fold more potently than it displaced the binding of ligands for 3 other transmitters present in the rat cerebral cortex.

$GABA_B$ receptors (see ref. 2 for review) have recently assumed additional importance because of evidence that they mediate both pre- and postsynaptic actions in brain that can be observed following synaptic activity in brain slices. For example, these receptors mediate a widespread postsynaptic potassium conductance in brain[7,8,19] (but see ref. 15) via G-proteins that are inactivated by pertussis toxin[20,21] and there are more recent indications that presynaptic γ-aminobutyric $acid_B$ ($GABA_B$) autoreceptors are responsible for the depression of GABA release that occurs during repetitive synaptic activity of GABAergic neurons in brain slice preparations[4,5,22].

In spite of this compelling evidence that $GABA_B$ receptors participate in the normal physiology of brain, studies of these receptors, in particular functional studies, have been hampered by the lack of suitable antagonists. This deficiency was only partly mitigated by the advent of the antagonist phaclofen; phaclofen is weak (IC_{50} for its antagonist activity is in excess of 200 μM[8,11]), can have agonist activity[11,15] and has effects that may not arise from its action at $GABA_B$ receptors[14].

Accordingly, we have employed binding assays to examine the specificity and certain other characteristics of 2-hydroxysaclofen (2-OH-saclofen), a recently available sulfonic acid analogue of baclofen that blocks some $GABA_B$ actions more potently than phaclofen has done[3,12].

Membrane preparation and binding assays were conducted according to previously published protocols[1,9,10,17]. Crude extensively washed synaptic membranes were prepared for [^{3}H]baclofen and [^{3}H]muscimol binding according to a procedure published by us[1], while crude membrane was prepared for the binding of [^{3}H]-OH-DPAT and [^{3}H]*N*-methyl-scopolamine according to procedures published by others[9,10,17]. Baclofen binding was to membranes that had been permeabilized by saponin (0.5%)[1], while binding of the other three ligands followed protocols published by others (see refs. 9, 10,17).

Binding assays for all radioligands were performed by filtration using GF/C Whatmann filters. Unless otherwise stated, binding data are expressed as the mean ± standard error of the mean of at least three independent experiments, each performed in triplicate. Saturation binding data were analyzed by the iterative computer program LIGAND[16].

(–)-Baclofen was given by Ciba-Geigy. 2-OH-Saclofen (3-amino-2-(4-chlorophenyl)-2-hydroxy-propylsulphonic acid) and muscimol (3-hydroxy-5-aminomethylisoxazole) were purchased from Research Biochemicals Inc.; phaclofen (3-amino-2-(4-chlorophenyl)-propylphosphonic acid) from Tocris Neuramin, U.K.; radioligands from New England Nuclear; all other reagents from Sigma.

To set a time of incubation with [^{3}H]baclofen that would be sufficient to allow equilibrium binding to be attained, we measured specific [^{3}H]baclofen binding as a function of time of incubation at 22 °C. Binding was clearly at equilibrium within 10 min of incubation either in the presence or absence of 2-OH-saclofen. A 15 min incubation period at 22 °C was adopted for this assay. To

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Rapid communication

$GABA_B$ receptor antagonism by resolved (*R*)-saclofen in the guinea-pig ileum

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Abstract

The $GABA_B$ receptor antagonist saclofen (3-amino-2-(4-chlorophenyl)propylsulphonic acid) has been resolved by chiral high-performance liquid chromatography. The enantiomer (*R*)-saclofen, but not (*S*)-saclofen, reversibly antagonised the (*R,S*)-baclofen-induced depression of cholinergic twitch contractions in the guinea-pig ileum with an apparent pA_2 of 5.3. Also, 2-hydroxy-saclofen was resolved by the same method, its (*S*)-enantiomer yielding an apparent pA_2 of 5.0. This method provides a convenient resolution of these antagonists.

Keywords: $GABA_B$ receptor; (*R,S*)-Baclofen; (*R*)-Saclofen

$GABA_B$ receptors are bicuculline-insensitive receptors for the inhibitory neurotransmitter GABA (4-aminobutanoic acid) that are stereospecifically activated by baclofen (4-amino-3-(4-chlorophenyl)butanoic acid), agonist activity residing in the (*R*)-enantiomer of known absolute configuration (Chang et al., 1982). Saclofen (3-amino-2-(4-chlorophenyl)propylsulphonic acid) and its hydroxy analogue 2-hydroxy-saclofen (3-amino-2-hydroxy-2-(4-chlorophenyl)propylsulphonic acid) are antagonists at these receptors, derived by making a sulphonic replacement of the carboxyl group of baclofen (Kerr and Ong, 1992). Recently, both saclofen and 2-hydroxy-saclofen have been resolved by chiral analytical high-performance liquid chromatography (Vaccher et al., 1993). This analytical chiral separation has been scaled up to provide a convenient method for preparative isolation (> 99%) of their respective enantiomers, using an analytical crown ether column (CR +) under isocratic conditions (detailed in Vaccher et al., 1996). We here show that antagonist activity at $GABA_B$ receptors of the guinea-pig ileum resides in the (*R*)-enantiomer of saclofen.

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$GABA_B$ receptor-mediated effects of baclofen, and the enantiomers of saclofen, were examined on repetitive cholinergic twitch contractions, evoked by field stimulation as previously described (Kerr et al., 1995). Concentration-response curves to baclofen, in the presence and absence of the antagonist were constructed, and the pA_2 value was derived from the relationship $pA_2 = \log (CR - 1) - \log [B]$, where $(CR - 1)$ is the concentration ratio − 1, and [B] the antagonist concentration. All numerical data on the concentration-response curves have been expressed as means ± S.E.M. The number of preparations used for each experiment was $n = 4$.

Baclofen-induced depression of ileal twitch contractions was reversibly antagonised by (*R*)-saclofen, which alone did not affect the amplitude of the twitch contractions, nor did it have any $GABA_A$ or $GABA_B$ partial agonist activity. (*S*)-Saclofen was inactive. As shown in Fig. 1, using (*R*)-saclofen (25 μM), the concentration-response curve for the depression of the twitch by (*R,S*)-baclofen was shifted 6.3-fold to the right, giving an apparent pA_2 of 5.3 for (*R*)-saclofen. By contrast, (*S*)-saclofen up to 200 μM showed no such antagonism of baclofen in this preparation. Also shown is a concentration-response curve for baclofen in the presence of (*S*)-2-hydroxy-saclofen (50 μM), resolved by the same method; this enantiomer yielded

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