Universidad Europea

TRABAJO DE FIN DE GRADO

Grado en Odontología

The role of AMPA receptors in orofacial pain

Madrid, curso 2020/2021

Número identificativo 234

Abstract

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor are tetrameric, cation-permeable ionotropic glutamate receptors that are expressed throughout the brain and have an essential role in the functioning of the brain. These receptors have shown a close association with pain. This review will specifically focus on orofacial pain, which is known to be pain in the head and neck region. The aim of this study is to create a complete review on the role of the AMPA receptors on orofacial pain and, also to determine if there is an association between the AMPA receptors and orofacial pain. To complete this review, information was taken from many different resources such as electronic databases which included; journals articles, books and some websites. Results have shown that the trafficking of AMPA receptor, their subunit composition, the process of phosphorylation and regulation of the subunits and all the interacting proteins, play a critical role in the nociceptive processing of the spinal cord. Out of all these processes the phosphorylation of the receptor plays a key role in the development of pain. Research has shown that AMPA receptors have a part in; stress, migraines and neurodegenerative diseases like amyotrophic lateral sclerosis (ALS) and craniofacial muscle pain which all consequently leads to orofacial pain. From the review conducted, it can be concluded that AMPA receptors does have role in the development of orofacial pain.

Summary

Los receptores del ácido α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) son receptores tetraméricos de glutamato inotrópicos permeables a los cationes que se expresan en todo el cerebro y tienen un papel esencial en el funcionamiento del cerebro. Estos receptores han mostrado una estrecha asociación con el dolor. Esta revisión se centrará específicamente en el dolor orofacial, que se conoce como dolor en la región de la cabeza y el cuello. El objetivo de este estudio es realizar una revisión completa sobre el papel de los receptores AMPA en el dolor orofacial y, también determinar si existe una asociación entre los receptores AMPA y el dolor orofacial. Para completar esta revisión, se tomó información de muchos recursos diferentes como bases de datos electrónicas que incluían; revistas, artículos, libros y algunos sitios web. Los resultados han demostrado que el tráfico del receptor AMPA, su composición de subunidades, el proceso de fosforilación y regulación de las subunidades y todas las proteínas que interactúan, juegan un papel crítico en el procesamiento nociceptivo de la medula espinal. De todos estos procesos, la fosforilación del receptor juega un papel clave en el desarrollo del dolor. La investigación ha demostrado que los receptores AMPA participan en; estrés, migrañas y enfermedades neurodegenerativas como la esclerosis lateral amiotrófica (ELA) y el dolor de los músculos craneofaciales que, en consecuencia conducen a dolor orofacial. De la revisión realizada, se puede concluir que los receptores AMPA sí tienen un papel en el desarrollo del dolor orofacial.

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1. Introduction

1.1. Definition and relevance of pain

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor [1] has shown a close association with pain.[2] This review will specifically focus on the association between the AMPA receptor and orofacial pain. Pain can be defined as an unbearable sensation and emotional experience an individual will feel. This can lead to actual or potential tissue damage that can compromise an individual's life. [3] Universally this is understood as the pointer in a disease which brings the patient to the physician's recognition. It is known to be the main mark of inflammation and damages to the tissue which consequently causes tissue protection and tissue repair.

A very important aspect of healthcare is the prevention and management of pain. Pain can come from any situation such as injury or trauma which is considered to be the main cause. Perception of pain is very subjective in every individual and is considered to be complex.

1.2. Classification of pain

There are many different variables which control pain, thus many different classifications for pain exist.[3] One way to classify pain is to differentiate it from being nociceptive pain or neuropathic pain.[4] We talk about nociceptive pain during the process in which the body reacts to a painful stimulus and no nerve damage is caused, whereas neuropathic pain is that in which there is nerve irritation, inflammation or neural tissue compression.

The experience of pain is very diverse and subjective to each individual therefore it can be difficult to classify pain in terms of this variable. However, pain can be separated into three categories, which are based on the initiating conditions and the anticipated underlying conditions. These three categories are: acute nociception, post tissue injury or inflammation and post nerve injury. [5] Acute nociception is crucial for survival; this is the warning signal for an individual or subject. With the removal of the stimulus the sensation of pain resolves.[5] For an example, if someone touches a hot plate the initial response would be to remove the hand from the plate due to acute nociception, and this will stop the sensation of pain. Tissue injury or inflammation causes pain due to continuous exposure to a high intensity stimulus. Even with the removal of the stimulus the sensation of pain continues. [5] Post nerve injury causes a state of pain in which there are components and persistency of hyperalgesia and allodynia.[5] Hyperalgesia is a condition in which an individual tends to have an increased sensitivity to the sensation of pain and thus leads to an elevated response. Whereas allodynia is a condition in which an individual feels the sensation of pain due to a stimulus that normally does not initiate pain. Both these conditions have been associated with distribution of the injured nerve. [5]

1.3. Orofacial pain

This review will focus specifically on orofacial pain, which is considered as a highly prevalent and incapacitating condition.[6] The orofacial region is complex that involves the hard and soft tissues of the head, oral cavity, neck and face thus pain can arise from many sources. [6][7] It can be difficult to categorize orofacial pain due to the

abundant and intricate innervation of the region, which may condition the therapeutic approach, and consequently the efficacy of the treatment.[8] This type of pain can develop due to diseases of the orofacial structures, musculoskeletal disorders, peripheral or central nervous system (CNS) disease or may be due to the manifestation of psychological disorders. [7] Currently there are many different types of classifications that exist for orofacial pain as the level of pain can be considered subjective and very diverse. Okeson [9] classified orofacial pain into two conditions; physical and psychological. The physical conditions included temporomandibular disorders (TMD), neuropathic pain and neurovascular disorders.[9] On the other hand, psychological conditions included disorders related to mood and anxiety, such as stress which can be a causing factor.[6] [10] For an example, some individuals when feeling stressed have shown to present certain habits such as bruxism, which can eventually lead to orofacial pain.

Furthermore, another way orofacial pain can be classified is due to the nature of the pain being acute or chronic. One of the most common reasons for the development of orofacial pain is due to dental problems which affects the lower part of the face, in general the pain is of acute nature.[8] However, among the different types of chronic pain include pain of the temporomandibular, myofascial muscles in conjunction with neuralgia. These are the types of pain with a chronic nature that have a higher incidence in the dental practice.[8] In the majority of cases the pain felt is related to the teeth, periodontal structures, mucosal structures and the surrounding tissues. Usually, in most cases the dental pain is due to the consequence of an inflammatory process of the pulp and the duration and intensity normally depends on the

magnitude of the damage. [8]However, there are some conditions present in which we can find the painful processes in the same structures but the pain may be derived from other extraoral locations.[8] This condition will usually be identified by the dentist performing a thorough medical history, asking all the correct questions and by performing an extra oral and intra oral examination. The dentist will look for bleeding, red and inflamed tissues and conduct tests such as taking X-rays, checking the probing depth and percussion, to help identify the origin of pain. It is also important to take into account that the diagnosis of orofacial pain can have a diverse origin such as dental, oral or even systemic. Additionally, pain can be influenced by other subjective sensations of the patient like anxiety. [8]Therefore, reaching a correct diagnosis can sometimes be difficult to achieve. Another cause of the orofacial pain in the general population is headaches such as migraines.[8]

Another type of orofacial pain is neuropathic pain, most commonly known as neuralgia. The etiology for this type of pain is usually unknown. [8] In the past, orofacial neuralgia was limited to the trigeminal nerve. [8] However, recently there have been new classifications for the study of different neuralgias such as trigeminal neuralgia, atypical trigeminal neuropathic pain, persistent idiopathic facial pain, neuralgia of the intermediate nerve of Wrisberg, neuralgia of the glossopharyngeal nerve, neuralgia of the superior laryngeal nerve, postherpetic neuralgia, atypical neurovascular pain and phantom tooth pain.[11][8] Out of all of these, trigeminal neuralgia is the most common and most difficult to treat, due to the fact that it can be present in a different location and have a different etiology in each case. [8] The

episode of pain can last from a few seconds to several minutes, and patients who suffer from this usually present peaks of pain in a constant manner. [8]

1.4. Pathway of pain

The pathway of pain involves the function of the afferent sensory nerves. These transfer different types of information or signals to the brain.[12] These sensory end organs contain receptors which respond to stimuli within the skin and tissues and this is where the pathway begins. The primary afferent fibers includes; A-delta (Aδ) thin myelinated fibers which conduct signals at a speed between 2 to 20 m/s and the C fibers which have the greatest presence in peripheral nerves, are unmyelinated and conduct at a speed less than 2 m/s. [12] Both the Aδ and C fibers have a great involvement in the development of pain. They are both activated in response to chemical, mechanical, intense cold or heath stimuli.[12] When activated they form a signal known as an electrical impulse or action potential. This occurs within the sensory nerve and is transferred to the nerve cell body inside the dorsal root ganglion of the spinal cord. The nerve synapses with a spinal cord cell, allowing the action potential signal to be transmitted to the brain through two different tracts: the spinothalamic and spinoparabrachial tract. [12]Transmission of the action potential signals in the brain involves synapses within the different parts of the brain which include: the medulla obolongata, thalamus, amygdala, limbic system or somatosensory cortex among others.[12]

1.5. Inflammation and pain

Orofacial pain is related to inflammation. This and trigeminal nerve injury are known to frequently cause persistent pain. Tissue inflammation arises due to continuous exposure to stimuli which retain high intensities leading to the sensation of pain that will continue even beyond the removal of the causing stimulus. [5] This type of pain typically ceases or patients recover from this after the injury state is treated.[5] Inflammation at the peripheral terminal also causes the activation of an innate immune cascade, which triggers the release of many different active factors that comes from the blood, injured cells and the local and migrating inflammatory cells.[5] These factors, which are released, will then stimulate C fibers. It will be achieved by action of the receptors that are located on the afferent terminal and will eventually sensitize these terminals.[5] There are many different systems which underlie the spinal facilitation, they include; increased postsynaptic transmission, local non-neuronal systems, loss of local inhibition and the movement of on non-neuronal inflammatory cells in the dorsal root ganglion.[5] This sensation of pain can migrate to the different parts of the orofacial region which are innervated by the non-injured trigeminal nerve branches consequently leading to orofacial pain. [13] During orofacial ectopic pain, the sensation of pain spreads from the injured branch regions to uninjured branch regions.[13] In the dental clinic this is usually common after incidences such as, inflammation of the pulp in a tooth or the extraction of a tooth. The pain in these cases will be persistent or continuous and will develop in the uninjured and non-inflamed parts of the orofacial regions, which can cause severe discomfort to the patient.[13]

Following trigeminal nerve injury, the primary afferent neurons are activated causing the generation of action potentials in the trigeminal ganglion neurons. These signals will then be passed to the CNS.[13]

Within the trigeminal ganglion neurons after the activation of the primary afferent neurons other activities will also be initiated such as nitric oxide (NO) signalling. [13] Expression of neuronal nitric oxide synthase (nNos) in the sensitized primary afferent neurons will increase the synthesis of NO. [13] Therefore, from the sensitized primary afferent neurons, NO is released or discharged. [13] NO signalling alters the activity like excitability in neurons, most commonly the neurons of the uninjured trigeminal nerve branches. [13] The activity of the injured neurons, together with the high excitability of uninjured neurons, will lead to the sensation of persistent or continuous pain.[13]

The primary afferent neuron consists of a soma that is tightly surrounded by satellite glial cells (SGCs) in the trigeminal ganglion.[13] These SGCs have shown to have an association with ectopic orofacial pain. Gap junctions are present in cells, these are also known as membrane channels which allow the movement of ions and other components between cell to cell. The primary components of gap junctions are Connexins, these can be categorised into two hemichannels, that are named connexons, which contributes to the binding of SGCs. [13] The primary gap junction protein is Connexin 43 (Cx43) and modulates transportation between the SGCs. [13] After a trigeminal nerve injury, Cx43 activates SGC which propagates throughout the trigeminal ganglion leading to the sensitization of uninjured trigeminal ganglions, that has a main involvement in ectopic orofacial pain.[13]

1.6. Glutamate signalling

A neurotransmitter considered to be very important in the excitatory synapses of the CNS and also have a vital part in the development of pain, is known as glutamate. [14] Glutamate has many different receptors such as; kainite, N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor.[14][15] The transmission of signals and information in the excitatory synapse mediated by glutamate, which is at the glutamatergic synapse, is shown to be determined by the number and function of the AMPA receptors. [2] Previous studies have shown that glutamate expression increased after peripheral nerve injury specifically at the dorsal root ganglion, demonstrating glutamate involvement in nociception. [16] Voltage-gated sodium channels (VGSCs) are required for the transmission of nerve impulses. Therefore, they are important for the excitability of neurons and play a critical role in controlling neurotransmitter release. [5]In the persistence of pain several VGSC are implicated such as, $Na_v1.3$, $Na_v1.7$ and $Na_v1.8$.[5] Increased levels of $Na_v1.7$ have been shown to be present after peripheral inflammation, which is regulated by cyclooxygenase (COX) dependent mechanism.[5] Additionally, the levels of $Na_v1.8$ has been elevated due to the stimulation by a number of inflammatory mediators. A disruption in this stimulation has ceased or abolished inflammatory pain.[5]

1.7. AMPA receptor

Structure of the AMPA receptor:

AMPA receptors have a tetrameric structure and are cation-permeable glutamate receptors. These receptors are widely present throughout the brain and have an

important role in its functioning.[17] [18]Also, these molecules consist of different combinations of four subunits which are: GluR1, GluR2, GluR3 and GluR4. The four different subunits have a very close association with somatosensory processing, due to the fact that they are widely expressed in the spinal dorsal horn. However, out of all the subunits GluR1 is particularly abundant in the superficial dorsal horn, specifically in laminae I-II and undetectable in the deeper dorsal horn laminae. [2] Whereas, the presence of GluR2 is observed all along the dorsal horn, especially at the inner lamina II where it is abundant and at the outer lamina II the presence is very scarce.[2] Also, tests have revealed that at the deep laminae III-IV of the dorsal horn there is scattered cell staining for GluR1, GluR2, GluR3 and GluR4.[2]

Traditionally, the AMPA receptors were classified into two groups: long tailed and short tailed. [18] The long tailed group consists of GluA1, GluA4 and a splice variant of GluA4, however the short tailed group consists of GluA2, GluA3 and a splice variant of GluA4.[18] The difference between these two groups is that the long tailed AMPA receptors are taken into synapses in a manner that depends on the activity, whereas the short tailed AMPA receptors undertake constitutive cycling in and out of the synapses.[18] Furthermore, it is also known that the long tailed AMPA receptors are directed to synapses in response to neuronal activity, for an example during the induction of long term potentiation (LTP). However the short tailed receptors are constitutively directed to synapses.[18]

Each of these subunits consists of around 900 amino acids and are composed of four different domains. These four domains include: extracellular amino terminal end,

ligand binding end, a receptor channel end and an intracellular C-terminal end**.** The structure of the receptor is presented on Figure 1**.**[2] [19]. Within the ligand binding domain, there are two polypeptide segments that work as recognition site of the agonist. [2] The receptor channel end contains three transmembrane domains (M1, M3 and M4), as well as a re-entrant loop inside the membrane (M2), which takes part in the creation of the ion channel pore.[2] The intracellular C-terminal end has a very crucial role in regulating the function of the receptor. Intracellular C-terminal end contains multiple sites for phosphorylation, for many different protein kinases. [2]

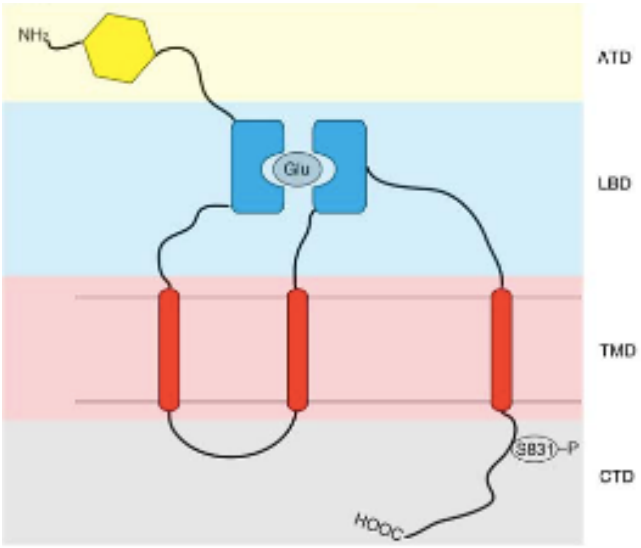

Figure 1: Image of an AMPA receptor subunit structure showing the four main domains. ATD represents the extracellular amino terminal domain, LBD stands for ligand binding domain, TMD are the transmembrane domain and CTD is the cytoplasmic carboxy-terminal domain. [19]

There is a diversity of C terminal intracellular tails of the AMPA receptors amongst the subunits. Additional variants are produced by RNA editing and alternative splicing. At the so-called “flip or flop exon”, alternative splicing results in subunit variants which have clear receptor desensitization properties. Out of all the various subunit combinations, GluR1 and GluR2 subunits are universally presented and are in most of the AMPA receptors in the adult mammalian CNS.[2]

Compared to other subunits, most of the GluR2 subunits are subjected to RNA editing, which ultimately replaces a glutamine for a positively charged arginine during the editing process. This occurs at the assembled channel at the pore forming region changing the structure of the receptor. The new GluA2 now contains arginine at a vital point in the pore forming M2 segment and results in a prevention of calcium influx due to a decrease in permeability for this ion.[1] This modification results in the receptors containing GluA2 to have a linear current voltage relationship. As a result, the adult brain hosts the majority of GluA2-containing AMPA receptors, which are mostly impermeable to calcium ions. Furthermore, they exhibit a lower unitary channel conductance and an increase in decaying process. On the other hand, AMPA receptors lacking GluA2 are permeable to calcium ions and express an increased conductance to a single, along with faster rise and decay kinetics.

Production and location of the AMPA receptor:

AMPA receptors are usually located at excitatory glutamatergic synapses and are situated across from the presynaptic zone on the postsynaptic membrane. It is here where the glutamate-filled vesicles fuse with the plasma membrane and eventually release their contents into the synaptic cleft. At a mature synapse, there is abundance of AMPA receptors, ranging from tens to hundreds. This corresponds well with the spinal size and the strength of the synapse. These receptors are extremely dynamic and have the characteristic of being laterally mobile on along the surface between synaptic and extra synaptic sites. In addition, another distinctive feature is that they have a short half-life of tens of minutes and undertake constitutive trafficking

to and from the cell surface. The efficacy of the synaptic transmission depends on the number of these receptors at the synapse.

Prior to reaching the synapses, the exchange AMPA receptors from the endoplasmic reticulum is modulated by various accessory proteins such as Cornichons and Transmembrane AMPA Receptor regulatory Proteins (TARPs). Each of these protein families include many different proteins. The best studied for TARPs include γ-2 (stargazin), γ-3, γ-4, γ-5, γ-7 and γ-8, and for the Cornichon-like protein is CNIH2/3.[18] If a deficit occurs in these proteins, it will lead to dysregulation in the exchanging process of the AMPA receptors, as well as their presentation at the synapses. Especially with TARPs, they are comprised of transmembrane domains, four to be precise and a C-terminal domain. They have been shown to stabilize the AMPA receptors both at the surface of the cell and at the synapses. [18]The positively charged C-terminal domain interacts intensely with membrane lipids, which causes the AMPA receptors to stabilise. A loss of TARPs leads to a decreased AMPA receptor expression suggesting that the AMPA receptor becomes unstable.[18] Kinesin and GRIP1 are responsible for the interactions of the AMPA receptors when they are being transported along the dendrites. Another way the receptors could be trafficked is through the plasma membrane at the soma where they can diffuse laterally into the cell surface to the synapses. It is most important to note that the mRNA coding for GluR1 and GluR2 AMPA receptor subunits can be found in the dendrites together with the protein translation machinery.

The AMPA receptors reach the synapse through a process of exocytosis. Many past and current studies have hypothesised that the soma, dendrite or directly the spine, are sites of insertion. The mechanism of action is started when the receptors reach the extra synaptic regions, they travel into the synapses where they are terminated or retained. Both these processes are regulated by neuronal activity. The SNARE (Soluble NSF Attachment protein Receptors) proteins are involved in the exocytosis of the AMPA receptors. Studies have also shown that there is a distinction in exocytosis properties between the different AMPA receptor subunits.
For example, the short tailed heterodimers (GluR2/3) travel in and out of the membrane, maintaining the surface pool of synaptic receptors. However, the long tailed subunits (GluR1/2 and GluR2/4) are inserted into synapses in an activity dependent manner.

Role of the AMPA receptor:

Glutamate binds to the AMPA receptor on the surface of the post synaptic cell membrane. When the receptor is activated it will allow calcium and sodium ions to pass into the postsynaptic cell, resulting in the depolarisation or reversal of the membrane potential. [14] The binding of glutamate and the AMPA receptor to the membrane acts as a mediator in majority of the fast excitatory currents in the CNS. This ultimately causes a depolarisation in the postsynaptic neuronal membrane to facilitate the production of action potentials.[14] The action of AMPA receptors acting by VGSCs could play a major role in pathological excitation leading to nociception. [20] These molecular events have shown a close association in the modulation and processing of pain [2]

2. Objectives

The primary objective of this study is to create a complete review about the role of AMPA receptors in orofacial pain. The secondary objective is to study if there is an association between AMPA receptors and orofacial pain.

3. Methodology

For this review, many different resources were used to conduct the research. Resources such as electronic databases included journals, articles, books and some websites.

Mainly electronic databases were searched for the majority of the information. These included: Medline (PubMed), Google Scholar and the electronic resources provided by Universidad Europea de Madrid. These were used to find studies and articles published from the year 2010 onwards to make sure the information was relevantly up to date. Search strategies were developed using the Boolean technique. The keywords included were: “pain”, “orofacial pain”, “pain pathway”, “AMPA receptor” and “glutamate”.

After the initial research process a strict inclusion and exclusion criteria using the language, publication date was followed to obtain the final selection of articles. The language that was chosen is English and the publication date was from the year

2010, so articles found published before 2010 was excluded. A final selection of 27 articles was used to conduct this review.

4. Discussion of results

From all the journals and articles that were studied, the majority of them have shown that the processes related to the AMPA receptors such as, trafficking, the modification of their subunit composition, the phosphorylation and regulation of the activity of the subunits and the availability of all the interacting proteins have a vital role at the spinal cord, especially during nociceptive processing. (1) More importantly, we should note that specifically in the CNS of the adult mammalian, the subunits GluR1 and GluR2 of the AMPA receptor are widely expressed, as compared to the other subunits.

A study by Galen et al. was conducted on mice models of visceral hyperalgesia.(1) Visceral hyperalgesia is a condition in which the subject has an increased sensitivity to pain in the internal organs, such as the face or stomach. Results showed that there was significant increase in trafficking of GluR1 present, especially in the spinal neurons. Within the spinal neurons information or signals were passed from the cytosol to the plasma membrane. (1)Therefore, this suggests that there is an involvement of AMPA receptor, especially its trafficking in spinal nociception causing an increased response to the sensation of pain.

In addition, a study on rats conducted by Chun et al. has demonstrated that peripheral AMPA receptors take part in causing muscle nociception, specifically they have a role in mediating craniofacial muscle pain.[21] Craniofacial muscle pain is known to be highly prevalent in TMD, which ultimately is a specific type of orofacial pain. [22]

The specific subunits of the AMPA receptors GluR1 and GluR2 have been shown to be present in the small and medium size neurons. However, the GluR2 subunits have a greater expression in the trigeminal ganglia in comparison to the other subunits. [21] Additionally, GluR2 is expressed more in the masseter afferents**.** [21] The masseter muscle is part of the facial musculature and is present on both sides of the face. It originates at the zygomatic arch and extends down to the mandibular angle, being part of the orofacial region. Cyanquixaline (CNQX) is an AMPA receptor antagonist; this was used in this study to conduct tests and revealed that the presentation of CNQX leads to a decreased amount of AMPA receptor induced responses, thus proving the importance of these receptors in acute pain conditions. [21]Furthermore, the study showed that AMPA receptors add to the initiation of the central trigeminal neurons and play a significant role in acute muscle pain conditions. [21] Therefore it is evident that the acute nociception of the muscle is partly facilitated by the AMPA receptors.

4.1. AMPA receptors and neurodegenerative diseases

Furthermore changing the composition of the AMPA receptor at certain points such as the spinal dorsal horn, through processes like GluR2 mRNA editing in diseases, can cause nociceptive responses.[1] For an example, dysfunctional GluR2 subunit editing of the AMPA receptor in the spinal cord of humans, results in a number neurodegenerative diseases like Amyotrophic Lateral Sclerosis (ALS).[1]

ALS is a progressive neurodegenerative disease which targets the nerve cells in the spinal cord, specifically at the lower and upper motor neurons. Additionally, it targets the brain and brainstem.[23] This disease is also known to be the most common cause of adult motor neuron disease, and has shown a very close association with chronic orofacial pain. [24] Patients with ALS have demonstrated a spinal onset causing referred weakness, muscle atrophy, fasciculations which affect the lower motor neurons and hyperreflexia and hypertonia which involve the upper motor neurons. [23] Sufferers of ALS have also shown progressive limitations at the masticatory functions, such as the opening of the mouth, which gets worse, leading to severe pain such as orofacial pain. [24] The maximum mandibular movement such as mouth opening, protrusion and laterotrusion and the bite force has been demonstrated to be significantly lower in ALS patients. [23]Furthermore there is a prevalence of TMD which leads to a certain type of orofacial pain in ALS patients. [23]This has shown that there is a relationship between the AMPA receptor, specifically the receptor containing the GluR2 subunit and orofacial pain.

4.2. AMPA receptors and migraines

There have also been links between the role of AMPA receptors and migraines. In addition, recent reports have revealed that migraines may be more common in orofacial pain, they have been considered to be a part of the neurovascular orofacial pain. [7] Migraines are a type of headache disorders, and among the different types of headaches this particular type is the best studied and described. They can either be continuous or episodic. [7] Typically, the pain caused by migraines is solitary and is felt around the ocular and the frontotemporal area. However, the sensation of pain can be experienced anywhere around the head or neck. The underlying pathophysiology of headaches and orofacial pain is thought to be due to the sensitization and stimulation of the components of the trigeminal ganglion. [7] Usually migraines tend to occur because of the provocation of trigger zones. These zones may be present in some parts of the face, and when stimulated can cause painful paroxysms.

In a study conducted by Liu et al. on a mouse model showed the importance of the contribution of the process of AMPA receptor phosphorylation in central sensitization during the transmission of pain.[25] Specifically, the phosphorylation of AMPA receptor at GluA1 Ser831 was increased after the intraperitoneal injection of nitroglycerin (NTG), which in turn caused acute migraine like pain. [25] Central sensitization is a process in which the effectiveness of the synapse is augmented on the somatosensory neurons, which are present in the dorsal horn of the spinal cord and in the sensory ganglia of the cranial nerves. The reason NTG was chosen is because it has previously been shown to trigger migraine attacks in migraine-

susceptible patients, as well as cause headaches in healthy people. The phosphorylation of the AMPA receptor occurs on the C-terminal part of the receptors, which contains many different sites for phosphorylation. This process is vital in causing modifications which are dependent on the activity, in synaptic processing of nociceptive information and also the central sensitization of the transmission of pain. The phosphorylation process switches the AMPA receptor from being calcium-impermeable to being calcium-permeable.[25] In this study, the phosphorylation of the AMPA receptor at the GluA1 Ser831 was measured in the spinal trigeminal nucleus caudalis (Sp5C), through a technique known as quantitative western blotting. Results showed that out of the four subunits of the AMPA receptors, GluA1 is present with the highest amount in the Sp5C. [25] Furthermore, this article demonstrates that the regulation of the AMPA receptor at the specific site GluA1 through the process of phosphorylation in the Sp5C plays a critical role in the molecular mechanism for migraine-like pain, which was provoked by NTG. [25] This was further proven by another test which involved mutations that targeted the AMPA receptor GluA1 Ser831 phosphorylation site. Here, different type of mice was used, they were AMPA receptor GluA1 S831A phospho-deficient mutants in which the normal site of phosphorylation was modified using a gene knock in technique. These results demonstrated that the mutation inhibits NTG-induced migraine-like pain.[25] Therefore, there is a clear link between AMPA receptors and migraines, which in turn leads to orofacial pain.

4.3. AMPA receptors and inflammation

Orofacial pain has also been associated with inflammation. Studies show that the trafficking of GluR2 and GluR3 of the AMPA receptor are involved in continuous inflammatory pain, which are present in the orofacial region. Within the activity of somatosensory processing, these two subunits are considered to be important. This process takes place at the spinal dorsal horn. Furthermore, the GluR2 subunit has shown to control AMPA receptor functions, these include synaptic plasticity, dendritic spine formation and most commonly trafficking**,** through specific interactions with intracellular molecules. In a study conducted on an animal pain model, it was reported that the N-ethylmaleimide sensitive fusion protein (NSF) is associated to the central sensitization of spinal cord neurons. This occurs by an alteration in the composition GluR2 subunit, resulting in peripheral inflammation. [(26)] There are connections that occur between the binding proteins and the C-terminal end proteins of the GluR2, these connections have shown to normalise or control the receptor internalization in the spinal dorsal horn neurons, which usually takes place in an inflammatory pain model. Regulation of the binding proteins occurs due to the GluR2 C-terminal undergoing phosphorylation by the specific protein kinase C.

Furthermore, in this study it was observed that in the AMPA receptor subunit knockout mice there was an enhancement of nociceptive plasticity that consequently lead to augmentation of inflammatory hyperalgesia.[(26)] On the other hand, GluR1 knockout mice have shown some deviations in the inflammatory pain indicating that GluR2 may be involved in continuous pain after the incidence of peripheral inflammation. [(26)] In addition, orofacial noxious stimulation is known to activate

second order nociceptive neurons, which are present in the subnucleus caudalis (Vc), spinal subnucleus interpolaris (Vi) and the transition zone which involves them both (Vi/Vc). [26] They are also present in the superior cervical spinal cord (C1/C2).[26] From the orofacial regions, the nociceptive neurons will receive signals considered to be noxious inputs. These are then all organised somatotopically within the orofacial regions.[26] After orofacial inflammation, it was noted that the excitability of the neurons of Vi/Vc, Vc and C1/C2 upon nociceptive signals was considerably greater and fields of reception of these nociceptive neurons was considerably greater too. [26] The results from this particular study by Honda et al. reveal the process of exchanging that takes place on membranes particularly involving the subunits GluR2 and GluR3, is also involved in increasing the neuronal excitability of Vi/Vc, Vc and C1/C2 in hyperalgesia. Furthermore, the results suggests that the trafficking of GluR3 trafficking maybe connected with inflammatory pain. [26] Trafficking of GluR2 and GluR3 is similarly also linked with the event of orofacial hyperalgesia as well as allodynia. These conditions are part the orofacial inflammatory pain conditions. [26] From this study, we can further confirm that a strong association exists between the AMPA receptor subtypes and orofacial persistent inflammatory pain.

4.4. AMPA receptors and stress

Stress can also induce the alteration of pain by the process of potentiation, which can be achieved by increasing the interactions of the AMPA receptor phosphorylation. Psychological conditions have been known to be a causing factor in orofacial pain, and stress can be a part of these psychological conditions. [6] The predisposition to stressful incidents can induce physiological and behavioural changes, and have been

shown to cause disruptions in long term adaptive responses. [10] Out of all the responses to a stressful incident, the main response is considered to be the quick activation of the autonomic nervous system. This leads to the rapid discharge of epinephrine and norepinephrine (NE) into the circulation.[10] Epinephrine and NE both act as neurotransmitters and hormones, they are responsible for the body's "fight or flight" response. The process of phosphorylation of AMPA receptors occurs at the C-terminal part of the receptor. NE has a key role in the intrinsic control of pain, through acting on the alpha 1 and alpha 2 adrenoreceptors. The relation NE has with AMPA receptor is that NE can enhance the AMPA receptor phosphorylation through the beta adrenoreceptor. [10] Furthermore, NE can stimulate the activation of cAMP dependent protein kinase A (PKA) and calcium or calmodulin dependent protein kinase II (CaMKII), these two protein kinases phosphorylate AMPA receptor GluA1 Ser831. [10] However, the GluA1 Ser845 is only phosphorylated by the PKA and not the CaMKII.[10] NE is a stress hormone that can stimulate the induction of GluA1 phosphorylation at both the Ser831 and Ser845 sites and so can enable long term potentiation (LTP) induction. The activation of the hypothalamus-pituitary-adrenal axis occurs due to stressful events, causing the release of glucocorticoids. Glucocorticoid is a type of corticosteroid hormone that comes from the adrenal glands. [10] The main glucocorticoid present in rodents such as mice is the corticosteroid. This can quickly and continuously control AMPA receptor GluA2 trafficking, which is known to have a crucial involvement synaptic transmission and plasticity. The induction or stimulation of the glucocorticoid receptors leads the hormone corticosteroid to efficiently condition the contents present within the synapse of the AMPA receptors and then consequently trigger the potentiation of the

synapse.[10] Therefore, hormones especially the ones released during stress, have been shown to play a role in the regulation of the AMPA receptor phosphorylation and trafficking, thus influencing the interactions and plasticity at the synapse. [10]

Also, there have been studies conducted to reduce traces of pain, by changing the composition specifically the subunits of the AMPA receptor, again proving the importance of this receptor during the sensation of pain.[27] To erase the sensation of pain low frequency stimulation (LFS) is used to condition primary afferents at the C fiber, which induces LTP at the C fiber synapses and changes AMPA receptor by modifying the state of phosphorylation on the receptor. [27] The process of phosphorylation of the AMPA receptor is known to be important in causing pain, and so the dephosphorylation of this receptor has been shown to reduce the trace of pain. Protein phosphatase 1 (PP1) can dephosphorylate the AMPA receptor. The dephosphorylation of the GluR2 subunit at Ser880 by PP1 causes a reduction of endocytosis of the AMPA receptors.[27] The specific reversal of these post synaptic memory traces of pain have shown the involvement of the state of phosphorylation of the AMPA receptor, and thus verifies the role of AMPA receptors have in pain.

A study by Li et al. conducted on mice has proven that by releasing stress hormones there is an alteration in the AMPA receptor phosphorylation and trafficking. [10] Stress has shown to regulate the AMPA receptor phosphorylation and trafficking, causing a modification in the structure of the AMPA receptor by altering the composition of the subunits. This change in the subunits composition leads to a switch of the AMPA receptor from being calcium-impermeable (containing GluA2) to becoming calcium-

permeable (lacking GluA2). [10] There will be an enhancement in calcium influx due to this switch and will further activate calcium-dependent protein kinases, eventually leading to the promotion of the phosphorylation of the AMPA receptor and other activities which are triggered by this phosphorylation process.[10] A positive feedback loop can be created, which has been shown to have some contribution to the molecular mechanisms that are present in stress-induced pain changes that occur after surgery. [10] It is also known that decreasing spinal calcium-permeable AMPA receptors causes a reduction in nociceptive plasticity. The opposite occurs when increasing the calcium-permeable AMPA receptor: there will be an acceleration of nociceptive plasticity. An acceleration of nociceptive plasticity can stimulate the action of LTP, which will consequently lead to a long lasting inflammatory hyperalgesia.[10] This again supports the view that AMPA receptors have a valuable role in the involvement of activity-dependent changes that occur within the synapse when processing nociceptive inputs.

The process of central sensitization is usually stimulated after tissue injury or nerve damage. Processes such as phosphorylation and trafficking of the AMPA receptor are considered very important in spinal central sensitization, especially in response to nociceptive stimulation. The consequent alterations in spinal central sensitization which may be long lasting and have a clear association with chronic pain development. [10]

In this study conducted by Li et al. they conducted tests by genetically modifying mice by a process of mutation, specifically knock in mutations were done.[10] These

mutations were designed at the specific sites Ser831 and Ser845 of the GluA1 to prevent the process of phosphorylation. [10] From this study we can observe that this mutation lead to disruptions in the plasticity of the synapse and learning, which is ideal in reduction of pain.[10] Another way to reduce pain is to lower the threshold for the induction of LTP and this can also be done by mutating the phosphorylation sites Ser831 and Ser845. This change in composition of the receptor has definitely shown to have an important role in pain. Additionally, results have shown that the targeted mutation of the GluA1 phosphorylation site at Ser880 blocks the occurrence of chronic inflammatory pain.[10] Results from this study have further proven that, the prolongation of incisional pain has been induced by stress and in this study the use of the mutant mice, which had the modification at the phosphorylation site has confirmed this. Further observations included that GluA1 phosphorylation at Ser831 site has an involvement in pain modification which is stimulated by stressful events. More specifically, the GluA1 phosphorylation is sufficient to reduce the threshold for spinal LTP induction.[10] Stress has been shown to control the phosphorylation of the AMPA receptor and this may be vital in spinal central sensitization and stress induced pain modifications.

To further investigate if stress activates the transition of pain by the potentiation of the AMPA receptor phosphorylation, Li et al. conducted tests using a calcium antagonist to permeable receptors.[10] The antagonist binds to the receptor to prevent the emergence of a response. Using the antagonist selectively reverses the secondary mechanical hyperalgesia in this study and does not have any effect on primary mechanical hyperalgesia in the plantar incision model. From this, we can

gather that secondary hyperalgesia, which is caused by central sensitization in postoperative patients, is regulated by the permeability of the AMPA receptors to calcium.[10] Whereas primary hyperalgesia which can be considered to be more severe resulting from actions such as creating an incision is not dependent on these receptors.[10] The results also demonstrated that the AMPA receptor regulated the LTP in the spine, and this was stimulated by subthreshold 10Hz activation in the AMPA receptor GluA1 S831D + S845D of the phosphomimetic mutant mice, again stressing the importance of phosphorylation in pain. [10] Also, NE amplified the process of spinal GluA1 phosphorylation. Therefore, it can be determined that particularly GluA1 phosphorylation has an important function in spinal central sensitization and the shift in pain stimulated by stress. [10] One of the underlying mechanisms of stress induced pain transition is due to the contribution of stress controlling the process of phosphorylation on AMPA receptor. By enhancing the phosphorylation of the AMPA receptor, additional signalling pathways may also be activated due to stress. This study has shown the involvement of stress and development of pain. It is also known that in stressful situations, people may develop certain habits such as clenching their teeth, grinding their teeth and even biting their nails. Continuously conducting these habits, can lead to TMD, which consequently will lead to orofacial pain by different mechanisms already described in this review.

4.5. Limitations of the study

From the research conducted, the majority of the results have proven that the AMPA receptors have a major function in the development and maintenance of pain. Furthermore, specifically related to orofacial pain some associations were found.

However, in this study there were some limitations such as the limited number of sources were evaluated. Also, most of the information found were results from tests conducted on mice, which may be different on humans. Therefore, more research and studies will be needed to be conducted.

5. Conclusion

In conclusion it is evident from the research conducted, that the AMPA receptors have a major role in the sensation of pain. Especially the trafficking of the AMPA receptor, their subunit composition, the process of phosphorylation and regulation of the subunits and all the interacting proteins, have a great function in the nociceptive processing at the level of the spinal cord.

The AMPA receptors are considered to be essential in the functioning of the brain. Changes in the post synaptic receptor are also thought to be fundamental mechanisms for most forms of synaptic plasticity.[18] The C-terminal end of the AMPA receptor subunits have been shown to contain a key role in the process of causing pain. From the research conducted, phosphorylation of the AMPA receptor is the main process that has led to pain. These phosphorylation sites are placed on the C-terminal ends of different AMPA receptor subunits and specifically the phosphorylation sites Ser831 and Ser845 of the GluA1 subunit have shown a greater importance. Furthermore, it was observed that AMPA receptors are associated to inflammatory pain, which is present in orofacial pain. The trafficking of the GluR2 and GluR3 has been shown to be involved in continuous inflammatory pain, present in

the orofacial region. It is clearly evident that the AMPA receptors have a very important role in pain.

There has been some evidence proving that there is an association between AMPA receptors and orofacial pain. Research has shown that AMPA receptors are modulated by: stress, migraines, neurodegenerative diseases like ALS and craniofacial muscle pain, all related to orofacial pain. However, more research and studies will be needed to further prove this association.

6. Responsibility

We have a social responsibility of improving the quality of a patient's life. From this current study conducted, I have a deeper and better understanding of pain. Also, I have understood the importance of managing pain in clinical practice, this has helped me in becoming a better healthcare professional. From all the knowledge I have gained through the research conducted, I will be applying this to improve the quality of a patient's life. In addition, I will try to be updated with future articles related to pain, so I can continuously provide patients with the better treatments.

Furthermore we can determine that more research will need to be conducted for the potential development of new treatments that can treat the sensation of pain. Therefore, we need to be aware of the economic responsibility as for research and development there will be more costs involved. As being part of the healthcare professionals, it is our responsibility to support research that can benefit patients.

Without research there is no information or new knowledge, so it is vital that we support researches conducted in the future.

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8. Annex

1. Regulation of AMPA receptors in spinal nociception.

Wang et al. Molecular Pain 2010, 6:5
http://www.molecularpain.com/content/6/1/5

MOLECULAR PAIN

REVIEW Open Access

Regulation of AMPA receptors in spinal nociception

Yun Wang[1,2], Jing Wu[3], Zhiguo Wu[1], Qing Lin[5], Yun Yue[1*], Li Fang[4,5*]

Abstract

The functional properties of α-amino-3-hydroxy-5-methy-4-isoxazole propionate (AMPA) receptors in different brain regions, such as hippocampus and cerebellum, have been well studied *in vitro* and *in vivo*. The AMPA receptors present a unique characteristic in the mechanisms of subunit regulation during LTP (long-term potentiation) and LTD (long-term depression), which are involved in the trafficking, altered composition and phosphorylation of AMPA receptor subunits. Accumulated data have demonstrated that spinal AMPA receptors play a critical role in the mechanism of both acute and persistent pain. However, less is known about the biochemical regulation of AMPA receptor subunits in the spinal cord in response to painful stimuli. Recent studies have shown that some important regulatory processes, such as the trafficking of AMPA receptor subunit, subunit compositional changes, phosphorylation of AMPA receptor subunits, and their interaction with partner proteins may contribute to spinal nociceptive transmission. Of all these regulation processes, the phosphorylation of AMPA receptor subunits is the most important since it may trigger or affect other cellular processes. Therefore, these study results may suggest an effective strategy in developing novel analgesics targeting AMPA receptor subunit regulation that may be useful in treating persistent and chronic pain without unacceptable side effects in the clinics.

Introduction

Glutamate synapses are involved in most excitatory neurotransmission in the central nervous system (CNS). The major glutamate receptor subtypes at glutamatergic synapses are currently subdivided into ionotropic glutamate receptors (ion channel forming) and metabotropic glutamate receptors (G-protein coupled). The former may include N-methyl-D-aspartate (NMDA) receptors and non-NMDA receptors, such as AMPA and kainite receptors. Cumulative evidence suggests that activity-dependent changes in the efficacy of glutamatergic synapses in pain transmission pathways greatly contribute to chronic pain caused by tissue damage or nerve injuries [1,2]. A great number of studies have addressed the role of NMDA receptors and metabotropic glutamate receptors in synapses between primary afferent fibers and spinal neurons. It has been demonstrated that the activation of NMDA receptors and metabotropic glutamate receptors critically contributed to the development of chronic nociceptive hypersensitivity following peripheral tissue damage or nerve injuries [1]. In contrast, the AMPA glutamate receptors are originally thought to mediate rapid excitatory neurotransmission in the CNS. Recently, more studies had supported the critical contributions of spinal AMPA receptors in the development of both acute and chronic painful responses [3-6].

AMPA receptors are widely distributed in the CNS. The functional properties and regulations of AMPA receptors in different brain regions, such as in the hippocampus (during long-term potentiation) and the cerebellum (during long-term depression), have been well studied both *in vitro* and *in vivo*. These studies suggest that the glutamate-mediated excitatory synaptic transmission efficiency is dependent on the number and function of AMPA receptors at glutamatergic synapses. The former is associated with the trafficking of AMPA receptors and the latter, is influenced by AMPA receptor subunit composition, post-transcriptional and post-translational modifications, and their interacting proteins [7-9]. Interestingly, several studies have shown that the trafficking of AMPA receptors, their subunits composition, phosphorylation regulation of AMPA receptor

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MOLECULAR PAIN

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3. Definition of pain and classification of pain disorders.

Journal of Advanced Clinical & Research Insights (2016), 3, 87–90

REVIEW ARTICLE

Definition of pain and classification of pain disorders

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Keywords
Classification, orofacial pain, pain definitions

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Received 16 December 2015;
Accepted 10 February 2016

doi: 10.15713/ins.jcri.112

Abstract

Pain of any origin comprises an individual's life. The prevention and management of pain is an important aspect of health care. Psychological factors play a key role in both onset and progress of any pain disorder. In pain disorders, pain is perceived in different anatomic locations such as lower back, head region, abdomen, and chest. Abnormal signal transmission and processing in the nervous system are the legitimate explanation for this condition. Although evidence suggests that pain disorder is widely prevalent in the general population, research still fails to address numerous aspects of pain diagnosis and management. Diagnostic criteria for pain differ in various Diagnostic and Statistical Manual of Mental Disorders (DSM) such as DSM-III, DSM-III revised, DSM-IV, and DSM-IV-textual revisions; hence, a more comprehensive classification is the need of the hour. The ability to understand and investigate the pathophysiologic process underlying a disorder depends on a valid, reliable classification system and common terminology to make effective communication among the academicians, clinicians, researchers, and patients. After the classification criteria are achieved, the validity and reliability of the criteria must be analyzed. Once the criteria have proven valid and reliable, research effort can be directed toward gaining better insight into prevalence, etiology, and natural course of a given disorder, eventually leading to more effective treatment. In this review, various definitions of pain along with few diagnostic classification systems for various pain disorders have been presented.

Introduction

The chore of medicine is to preserve and restore patient's health and to minimize their suffering. To achieve these goals, intellection about pain is must because pain is universally understood as a pointer of disease and it brings the patient to the physician recognition. Pain can originate from any situation, injury being the major cause. The pain perception in every individual is complex and is controlled by a variety of variables.

The main function of the sensory system in our body is to guard and keep up pain homeostasis. It does this by identifying, localizing, and recognizing the tissue damaging processes. In view of the fact that different diseases produce distinctive patterns of tissue damage. The location, the time course, quality, and tenderness provide important clues for diagnosis, which are used as one of the best hints to evaluate the response to treatment. Once the information is collected, physician can easily provide immediate and successful pain relief to the patient.[1]

In Greek word, pain means penalty. Plato said that pain arises from within the body and indicating that pain is more of an emotional experience.

In recent times, the concept of pain has evolved from one-dimensional to a multi-dimensional entity involving sensory, cognitive, motivational, and affective qualities. Pain is always subjective and every individual use this word through their previous experience related to the injury. Over time, various definitions have been given to describe and understand this pain in medical literature.[2] The aims of this review is to enlist various definitions of pain and few diagnostic classification systems for various pain disorders.

Pain Definitions

1. Task force on taxonomy of the International Association for the Study of Pain (IASP) says that pain is "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[3]
2. The North American Nursing Diagnosis Association defines that pain is a state, in which an individual experiences and reports severe discomfort or an uncomfortable sensation;

4. International spinal cord injury pain classification. Part I. Background and description.

Spinal Cord (2012) 50, 413–417

www.nature.com/sc

ORIGINAL ARTICLE

International Spinal Cord Injury Pain Classification: part I. Background and description

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Study design: Discussion of issues and development of consensus.
Objective: Present the background, purpose, development process, format and definitions of the International Spinal Cord Injury Pain (ISCIP) Classification.
Methods: An international group of spinal cord injury (SCI) and pain experts deliberated over 2 days, and then via e-mail communication developed a consensus classification of pain after SCI. The classification was reviewed by members of several professional organizations and their feedback was incorporated. The classification then underwent validation by an international group of clinicians with minimal exposure to the classification, using case study vignettes. Based upon the results of this study, further revisions were made to the ISCIP Classification.
Results: An overall structure and terminology has been developed and partially validated as a merger of and improvement on previously published SCI pain classifications, combined with basic definitions proposed by the International Association for the Study of Pain and pain characteristics described in published empiric studies of pain. The classification is designed to be comprehensive and to include pains that are directly related to the SCI pathology as well as pains that are common after SCI but are not necessarily mechanistically related to the SCI itself.
Conclusions: The format and definitions presented should help experienced and non-experienced clinicians as well as clinical researchers classify pain after SCI.
Spinal Cord (2012) **50,** 413–417; doi:10.1038/sc.2011.156; published online 20 December 2011

Keywords: classification; pain; spinal cord injury; nociceptive; neuropathic

INTRODUCTION

The purpose of the International Spinal Cord Injury Pain (ISCIP) Classification is to offer a method for classifying pain reported by persons with spinal cord injury (SCI), where pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[1]

Although there is consensus in the medical community that pain after SCI is common, there has historically been no consensus on how to define and classify it. This has led to an ever-increasing number (over 29 by 2002) of different classification schemes reported in the literature.[2] As classifications are built upon definitions, and prevalences of pain types are calculated based upon identified defined pain types, it should not be surprising that there are widely varying estimates of the prevalence of various types of pain after SCI. For example, the prevalence of visceral pain has been estimated to be in the range from 5 to 34%,[3–5] whereas the prevalence of neuropathic pain thought to be due to spinal cord damage and experienced below the level of injury has been estimated to be anywhere from 14 to 40%.[4–7]

Some of the variance in the reported prevalences is presumably due to methodological aspects of study design, for example, the time that has elapsed since injury at the point when a question on the presence of pain is asked, the threshold of intensity or discomfort at which pain or severe pain is defined, and questionnaire response rates or skewed population sampling. Estimates of the overall prevalence of pain after SCI range from 25 to 96%,[8] whereas for severe pain, the prevalence ranges from 30 to 51%.[9] However, a key problematic aspect is the lack of consistent definitions of SCI pain categories, which makes comparisons between studies difficult even if the other aspects of the design are controlled for.[9] This is most evident in differentiating between subtypes of pain of somewhat similar presentation, for example, visceral pain and neuropathic abdominal pain or pain due to nerve

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Development of the International Spinal Cord Injury Pain Classification was made possible by a grant from the Paralyzed Veterans of America, Washington DC to Mount Sinai School of Medicine.
Received 9 August 2011; revised 10 November 2011; accepted 11 November 2011; published online 20 December 2011

5. A brief comparison of the pathophysiology of inflammatory versus neuropathic pain.

Published in final edited form as:
Curr Opin Anaesthesiol. 2011 August ; 24(4): 400–407. doi:10.1097/ACO.0b013e32834871df.

A brief comparison of the pathophysiology of inflammatory versus neuropathic pain

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Abstract

Purpose of review—The aetiologies of inflammatory pain and neuropathic pain are fundamentally different. There are, however, common mechanisms underlying the generation of each pain state. We will discuss some specific elements observed in both tissue and nerve injury pain states and consider the hypothesis that these two states actually demonstrate a convergence over time.

Recent findings—The increased pain sensation following tissue and nerve injury results from several mechanisms, including altered ion channel expression in DRG neurons, enhanced dorsal horn glutamate release from primary afferents, enhanced glutamate receptor function in second order neurons, disinhibition in the dorsal horn and glia cell activation. The role of specific subtypes of receptors, ion channels and glutamate transporters is revealed at peripheral and central sites. Importantly over time, a number of changes, in the dorsal root ganglion and in dorsal horn observed after tissue injury resemble changes observed after nerve injury.

Summary—Recognition of mechanisms common to both inflammatory pain and neuropathic pain might shed light on the understanding of the transition from acute pain to persistent pain.

Keywords

tissue injury; nerve injury; DRG; dorsal horn

Introduction

Heuristically, the pain experience has been divided into three principal categories based on the initiating conditions and the anticipated underlying mechanisms: Acute nociception, post-tissue injury/inflammation and post-nerve injury.

1. Acute nociception

Acute (transient) high intensity stimuli yield a somatotopically limited pain sensation that resolves upon the removal of the stimuli. The acute pain sensation is crucial to survival (witness the perilous existence of those who have no such acute sensation [1]). The encoding of the stimulus involves specific activation of subpopulations of fast-conducting, lightly

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6. Orofacial pain management: current perspectives.

Journal of Pain Research

Dovepress
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REVIEW

Orofacial pain management: current perspectives

This article was published in the following Dove Press journal:
Journal of Pain Research
21 February 2014
Number of times this article has been viewed

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Abstract: Some of the most prevalent and debilitating pain conditions arise from the structures innervated by the trigeminal system (head, face, masticatory musculature, temporomandibular joint and associated structures). Orofacial pain (OFP) can arise from different regions and etiologies. Temporomandibular disorders (TMD) are the most prevalent orofacial pain conditions for which patients seek treatment. Temporomandibular disorders include a number of clinical problems that involve the masticatory musculature, the temporomandibular joint (TMJ) or both. Trigeminal neuropathic pain conditions can arise from injury secondary to dental procedures, infection, neoplasias, or disease or dysfunction of the peripheral and/or central nervous system. Neurovascular disorders, such as primary headaches, can present as chronic orofacial pain, such as in the case of facial migraine, where the pain is localized in the second and third division of the trigeminal nerve. Together, these disorders of the trigeminal system impact the quality of life of the sufferer dramatically. A multidisciplinary pain management approach should be considered for the optimal treatment of orofacial pain disorders including both non-pharmacological and pharmacological modalities.

Keywords: pain, orofacial, neuropathic, TMD, trigeminal, headache

Orofacial pain disorders

Orofacial pain disorders are highly prevalent and debilitating conditions involving the head, face, and neck. These conditions represent a challenge to the clinician since the orofacial region is complex and therefore, pain can arise from many sources. The clinician needs to have solid knowledge of the pain conditions that arise from these structures for proper diagnosis and a multidisciplinary approach of management is strongly recommended.

The orofacial pain classification as outlined by Okeson[1,2] is divided into physical (Axis 1) and psychological (Axis 2) conditions. Physical conditions comprise temporomandibular disorders (TMD), which include disorders of the temporomandibular joint (TMJ) and disorders of the musculoskeletal structures (eg, masticatory muscles and cervical spine); neuropathic pains, which include episodic (eg, trigeminal neuralgia [TN]) and continuous (eg, peripheral/centralized mediated) pains and neurovascular disorders (eg, migraine). Psychological conditions include mood and anxiety disorders. This review focuses on the current perspectives in orofacial pain management, and only TMD, neuropathic pains, and headaches will be discussed. For a more comprehensive discussion about pathophysiology and diagnosis of the disorders depicted in this classification and other painful disorders arising from the head, face, and neck, other texts should be reviewed.

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7. Orofacial pain and headache: A review and look at the commonalities topical collection on uncommon headache syndromes.

Curr Pain Headache Rep (2014) 18:400
DOI 10.1007/s11916-013-0400-5

UNCOMMON HEADACHE SYNDROMES (J AILANI, SECTION EDITOR)

Orofacial Pain and Headache: A Review and Look at the Commonalities

Steven D Bender

Published online: 6 February 2014

Abstract Headache and facial pain – in particular, temporomandibular disorders (TMDs) – are very prevalent conditions in the general population. TMDs are defined as a collection of symptoms and signs involving masticatory muscles, the temporomandibular joints (TMJs), or both. The pain reported by TMD patients is typically located in the muscles of mastication, in the preauricular area, or in the TMJs. In many cases, headaches and facial pain will occur in the same patient. Much of the research relative to the relationship of these disorders focuses on statistics of association and prevalence data. This review will provide a brief description of the types and classifications of orofacial pains (OFPs), as well as point to relevant research describing the commonalities and potential comorbid nature of these maladies. Finally, several recent papers describing morphologic changes to the brain in headache and TMD individuals will be discussed in an effort to stimulate further research into the potential common pathophysiologic mechanism that may explain the comorbid nature of these disorders.

Keywords Temporomandibular joint disorders · Orofacial pain, Migraine · Headache · Comorbid · Pain · Dental · Neurovascular · Musculoskeletal · Sleep bruxism · Trigeminal · Glia

This article is part of the Topical Collection on *Uncommon Headache Syndromes*

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Introduction

Headache is a common experience in the general population that potentially represents the summation of various stimuli converging in the central nervous system [1]. Sensitization and stimulation of the components of the trigeminal ganglion are thought to play an important part in the underlying pathophysiology of headache and facial pain disorders [2–4]. Among the primary headache disorders, migraine is the best studied and described. It is a prevalent and disabling condition that affects 35 million individuals in the U.S. alone [5]. Recent reports haves suggested that migraine and other headaches disorders may be more common in the orofacial pain (OFP) patient population [6, 7]. Apart from headache disorders, OFP also appears to be a common occurrence in both general and clinical populations. Epidemiologic studies have demonstrated the prevalence of OFP as 22 % of individuals in the United States over 18 years of age[8]. In another study, it was found that up to 25 % of a community population reported some form of OFP, with the highest prevalence in the 18–25-year-old age group. Temporomandibular disorders (TMDs), a sub classification of OFP, have an estimated prevalence of 3–15 % for Western populations [9]. Headaches, including migraine, appear to be more common in patients with TMD as compared to controls [10]. This article will provide a review of OFP with a special emphasis on temporomandibular disorders and will discuss how these issues may play a role in headache, as evidenced by current research findings.

Orofacial Pain

OFP is a term that often refers to pain associated with the hard and soft tissues of the head, face, oral cavity, and neck. OFP may be due to disease of the orofacial structures, musculoskeletal disorders or disease, peripheral or central nervous system

8. Dolor orofacial en la clinica odontológica.

RESED
Revista de la Sociedad Española del Dolor

REVISIÓN

DOI: 10.20986/resed.2019.3724/2019

Dolor orofacial en la clínica odontológica

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ABSTRACT

Most dental consultations are related to intraoral pain disorders affecting dental, periodontal and mucosal structures. Although the originating cause of pain and the anatomical structure frequently co-localise, orofacial pain and particularly oral pain are sometimes referred. That is, pain may be caused by extraoral processes out of the maxillofacial territory. Likely, some intraoral conditions such as an occlusal imbalance may also affect extraoral structures, leading to tension and pain on the neck, head, and back. Orofacial pain research is however an emerging discipline in comparison to other anatomical regions. This may be due, in part, to the fact that oral pain tends to recede over time or after tissue healing –in case there was an injury–. Notwithstanding, half of the patients reporting any sort of orofacial pain suffers chronically. And unlike acute receding pain, chronic pain is no longer a symptom, but a difficult-to-manage pathology, with scarce or none relation to the mechanisms that caused it. Moreover, the lack of appropriate anamnesis and clinical examinations, inaccurate pain syndrome nomenclatures or difficulty in diagnosis hamper sometimes an optimal therapeutic approach. Most oral pain classifications are still based on the affected anatomical structure rather than on the nociceptive mechanism itself. On the other hand, the precise aetiology of most of the so-called atypical algiae or the burning mouth syndrome is still unknown. The present review article aims to describe the main reasons for pain consultation at the dental clinic, with particular emphasis on the type of pain from a mechanistically point of view: nociceptive, inflammatory, neuropathic, psychogenic or mixed.

Key words: Orofacial pain, neuralgia, odontalgia, oral cancer, temporomandibular joint pain.

RESUMEN

La mayor parte de las consultas odontológicas están relacionadas con dolores intraorales que afectan a estructuras dentarias, periodontales y mucosas. Aunque generalmente la causa originaria del dolor y la estructura afectada coinciden en la localización, en ocasiones el dolor orofacial y, particularmente, el dolor oral, es referido. Esto es, el dolor puede deberse a procesos de origen extraoral localizados fuera del territorio maxilofacial. De igual manera, determinados trastornos orales, como un desequilibrio oclusivo, pueden afectar también estructuras extraorales, ocasionando tensión y dolor en cuello, cabeza y espalda. La investigación en dolor orofacial es, sin embargo, una disciplina emergente en comparación con otras áreas anatómicas, quizás debido, en parte, a que el dolor tiende a remitir con el tiempo o con la sanación del tejido afectado (si hubiera una lesión). Sin embargo, la mitad de los pacientes con algún tipo de dolor orofacial lo sufre de manera crónica y, a diferencia del dolor agudo, remitente, el dolor crónico no es ya un síntoma, sino una patología de difícil manejo, con escasa o ninguna relación con los mecanismos que lo originaron. Además, la falta de una adecuada anamnesis y exploración clínica, nomenclaturas inapropiadas o la dificultad de diagnóstico, hacen complicado en ocasiones un óptimo abordaje terapéutico. La mayoría de las clasificaciones de dolor oral siguen atendiendo a la estructura anatómica afectada más que al propio mecanismo nociceptivo. Por otra parte, la etiología exacta de muchas algias denominadas atípicas o del síndrome de boca ardiente sigue siendo desconocida. Esta revisión pretende describir los principales motivos de consulta por dolor en la clínica dental, poniendo particular énfasis en el tipo de dolor desde el punto de vista de su mecanismo: nociceptivo, inflamatorio, neuropático, psicogénico o mixto.

Palabras clave: Dolor orofacial, neuralgia, odontalgia, cáncer oral, dolor articular temporomandibular.

Recibido: 18-02-2019
Aceptado: 23-04-2019

Migueláñez Medrán BC, Goicoechea García C, López Sánchez A, Martínez García MA. Dolor orofacial en la clínica odontológica. Rev Soc Esp Dolor 2019;26(4):233-242.

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9. The classification of orofacial pains.

ELSEVIER
SAUNDERS

Oral Maxillofacial Surg Clin N Am 20 (2008) 133–144

ORAL AND
MAXILLOFACIAL
SURGERY CLINICS
of North America

The Classification of Orofacial Pains

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Pain diagnosis

This article is dedicated to the subject of orofacial pain and dysfunction. The orofacial structures are complicated, so there are many sources that can produce pain. It is imperative that the clinician be able to identify the precise source of pain to be effective in its management. This process is called "diagnosis" and is the most critical task for the clinician, for only by establishing the correct diagnosis can the appropriate and successful therapy be selected. Diagnosis is by far the most difficult aspect of managing a patient's pain problem. Because of this difficulty, many therapists fail to make the proper diagnosis. In fact, the majority of treatment failures arise directly from misdiagnoses. This article presents a means of assessing the pain complaint and describes a diagnostic road map that will lead the examiner toward an accurate classification of the pain disorder.

There are many methods by which pain disorders can be classified. The most elementary classification of pain is that which lists the anatomic locations where pain is felt. An example of such a classification would be head and neck pain, thoracic pain, abdominal pain, or extremity pain.

Subdivisions of head and neck pain would include orofacial pains, headaches and cervical pains. This article primarily discusses orofacial pains; however, the clinician must have an appreciation for other pain conditions of the head and neck so that proper diagnosis is possible. Other texts should be reviewed for a more complete understanding of headaches and cervical pain disorders.

A simple classification of pain disorders is often used to record the patient's subjective complaint. For example, it might list the complaint as a headache, toothache, chest pain, backache, or leg pain. It should be understood, however, that this type of classification identifies only the site where pain is felt, not the location of its true source. A pain listed as a "toothache" could be of dental origin and require dental therapy. But it could also be a heterotopic manifestation of some myogenous, vascular, or neuropathic condition that would require treatment using a completely different strategy. Therefore, such a classification has very little diagnostic or therapeutic value.

More refined pain classifications require additional knowledge of pain behavio and require a greater diagnostic effort. To classify pain by the location of its source requires an understanding of heterotopic pains and entails the need for diagnostic differentiation between primary pain and its secondary effects. Thus, "toothache" in such a classification might become pulpal pain, periodontal pain, or heterotopic pain when its true site of origin is determined. It should be obvious that this more accurate classification of the patient's complaint implies important therapeutic considerations.

In 1988, the International Headache Society published the first edition of the "Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain" [1]. In 2004, this classification was revised [2]. This classification attempts to separate all headaches according to etiology and involved structures. Although this classification has been most useful in unifying

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1042-3699/08/$ - see front matter
doi:10.1016/j.coms.2007.12.009

10. Stress induces pain transition by potentiation of AMPA receptor phosphorylation.

Cellular/Molecular

Stress Induces Pain Transition by Potentiation of AMPA Receptor Phosphorylation

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Chronic postsurgical pain is a serious issue in clinical practice. After surgery, patients experience ongoing pain or become sensitive to incident, normally nonpainful stimulation. The intensity and duration of postsurgical pain vary. However, it is unclear how the transition from acute to chronic pain occurs. Here we showed that social defeat stress enhanced plantar incision-induced AMPA receptor GluA1 phosphorylation at the Ser831 site in the spinal cord and greatly prolonged plantar incision-induced pain. Interestingly, targeted mutation of the GluA1 phosphorylation site Ser831 significantly inhibited stress-induced prolongation of incisional pain. In addition, stress hormones enhanced GluA1 phosphorylation and AMPA receptor-mediated electrical activity in the spinal cord. Subthreshold stimulation induced spinal long-term potentiation in GluA1 phosphomimetic mutant mice, but not in wild-type mice. Therefore, spinal AMPA receptor phosphorylation contributes to the mechanisms underlying stress-induced pain transition.

Key words: **AMPA receptor phosphorylation; pain transition; stress**

Introduction

Pain is a hallmark of tissue damage and inflammation, which promotes tissue protection and thereby contributes to repair. Thus, transient acute pain is an important feature of the adaptive response to damage. However, pain can persist for months or years after surgery even though the surgical incision that originally caused the pain has healed. Such chronic pain is maladaptive because it no longer serves as a protective reaction. To date, the neurobiological mechanisms that underlie the transition from adaptive acute pain to maladaptive chronic pain are not fully understood (Mifflin and Kerr, 2014).

Previous studies have shown that psychosocial and socioenvironmental factors contribute to the development of chronic postsurgical pain (Kehlet et al., 2006; Katz and Seltzer, 2009). Psychosocial stress is generally defined as any conditions that disturb the physiological or psychological homeostasis of an organism (Kim and Diamond, 2002; Krugers et al., 2010). Exposure to stressful events induces physiological and behavioral changes that promote long-term adaptive responses to such disturbances (Krugers et al., 2010). One of the core reactions in response to a stressful event is the rapid activation of the autonomic nervous system and subsequent release of epinephrine and norepinephrine (NE) into the circulation (de Kloet et al., 2005). NE can activate cAMP-dependent protein kinase A (PKA) and calcium/calmodulin-dependent protein kinase II (CaMKII; Hall, 2004; Wang et al., 2004b). AMPA receptor GluA1 Ser831 is phosphorylated by CaMKII and PKC, whereas GluA1 Ser845 is phosphorylated by PKA (Roche et al., 1996; Barria et al., 1997; Mammen et al., 1997). Genetically modified mice with knock-in mutations that block phosphorylation at the Ser831 and Ser845 sites of GluA1 show disturbances in synaptic plasticity and learning (Lee et al., 2003). Thus, the stress hormone NE can induce GluA1 phosphorylation at Ser831 and Ser845 sites, and thereby facilitate long-term potentiation (LTP) induction (Hu et al., 2007). Phosphorylation at these sites is necessary and sufficient to lower the threshold for GluA1 synaptic incorporation during LTP (Hu et al., 2007). In addition, stressful events stimulate the hypothalamus–pituitary–adrenal axis, and glucocorticoids, a type of corticosteroid hormone, are released from the adrenal glands after exposure to a stressful event (de Kloet et al., 2005). Corticosterone (Cort) is the main glucocorticoid in rodents, and can rapidly and persistently regulate AMPA receptor GluA2 trafficking, which is crucially involved in synaptic transmission and plasticity (Groc et al., 2008; Krugers et al., 2010). Glucocorticoid receptors

Received May 26, 2014; revised Aug. 28, 2014; accepted Sept. 3, 2014.

Author contributions: R.L.H. and F.T. designed research; C.L., Y.Y., S.L., and F.T. performed research; C.L., Y.F., S.L., H.F., Y.Z., O.F., J.S., Y.X., R.A.J., R.L.H., and F.T. analyzed data; R.L.H. and F.T. wrote the paper.

This work was supported by the National Institute of Dental and Craniofacial Research R01 Grant DE022888 (F.T. and R.L.H.) and the Blaustein Pain Research Fund (F.T.).

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DOI:10.1523/JNEUROSCI.2130-14.2014

 0270-6474/14/3413737-10$15.00/0

11. Persistent idiopathic facial pain.

Review

Cephalalgia
International Headache Society

Cephalalgia
2017, Vol. 37(7) 680–691

DOI: 10.1177/0333102417706349
journals.sagepub.com/home/cep
SAGE

Persistent idiopathic facial pain

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Abstract

Background: Persistent idiopathic facial pain (PIFP) is a chronic disorder recurring daily for more than two hours per day over more than three months, in the absence of clinical neurological deficit. PIFP is the current terminology for Atypical Facial Pain and is characterized by daily or near daily pain that is initially confined but may subsequently spread. Pain cannot be attributed to any pathological process, although traumatic neuropathic mechanisms are suspected. When present intraorally, PIFP has been termed 'Atypical Odontalgia', and this entity is discussed in a separate article in this special issue. PIFP is often a difficult but important differential diagnosis among chronic facial pain syndromes.

Aim: To summarize current knowledge on diagnostic criteria, differential diagnosis, pathophysiology and management of PIFP.

Methods: We present a narrative review reporting current literature and personal experience. Additionally, we discuss and differentiate the common differential diagnoses associated with PIFP including traumatic trigeminal neuropathies, regional myofascial pain, atypical neurovascular pains and atypical trigeminal neuropathic pains.

Results and conclusion: The underlying pathophysiology in PIFP is still enigmatic, however neuropathic mechanisms may be relevant. PIFP needs interdisciplinary collaboration to rule out and manage secondary causes, psychiatric comorbidities and other facial pain syndromes, particularly trigeminal neuralgia. Burden of disease and psychiatric comorbidity screening is recommended at an early stage of disease, and should be addressed in the management plan. Future research is needed to establish clear diagnostic criteria and treatment strategies based on clinical findings and individual pathophysiology.

Keywords

IFP, daily pain, trigeminal neuralgia

Date received: 30 January 2017; revised: 26 March 2017; accepted: 31 March 2017

Definition

The International Classification of Headache Disorders (ICHD, version 3) published by the International Headache Society (IHS) describes persistent idiopathic facial pain (PIFP) as 'persistent facial and/or oral pain, with varying presentations but recurring daily for more than 2 hours per day over more than 3 months, in the absence of clinical neurological deficit' (1). PIFP is the current diagnostic terminology that historically would have been considered under the name of atypical facial pain (AFP).

The diagnostic criteria for PIFP include the presence of daily or near daily pain that is initially confined but may subsequently spread (1). Pain cannot be attributed to any pathological process for a diagnosis of PIFP, see Table 1. Clearly this is a loose and ambiguous definition, and may allow the misclassification of a large number of chronic facial pain disorders. As such it is often regarded as a 'waste basket' diagnosis and one of exclusion. However, it is important for clinicians to clearly distinguish PIFP from other persistent orofacial pain disorders that may mimic it, such as trigeminal neuralgia with persistent background pain, painful traumatic trigeminal neuropathies, myofascial pain and others (2). Accurate diagnosis is key to successful therapy and prevents potentially serious consequences. Currently, the prevalent theory is that PIFP is a disproportionate reaction to a mild injury, but the exact pathophysiology is still unclear.

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12. Pain: Pathways and Physiology.

Pain: Pathways and Physiology

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KEYWORDS

• Pain • Neuropathic pain • Chronic pain • Acute pain

KEY POINTS

- Pain is a multifactorial process that may not always be linked to a stimulus and does not always directly correlate with the severity of injury.
- The pain pathways are constantly modulated through physical, biochemical, and psychological interactions.
- To optimize the treatment of pain, it is necessary to understand the anatomy and physiology of pain so that targeted therapies may be developed and used.

INTRODUCTION

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage".[1] Pain is often difficult to measure and assess accurately because of its subjectivity where sensation experienced by any one individual has both physical and emotional overtones. Pain, however, is a vital protective sensory phenomenon essential to survival. Patients with leprosy or congenital insensitivity to pain are prone to repeated tissue and organ injuries. Generally, pain is elicited from any stimulus that damages tissue or potentially damages tissue. Pain alerts the individual pathologic affronts on the body and possibly permits avoidance of the offending pathogen or stimulus. However, when the signaling becomes aberrant and chronic, the sensation of pain becomes detrimental to the individual, both physically and psychological. Although in this review the authors describe the physiologic pathways involved in pain, it is important to understand that pain is not always tied to a stimulus. In addition, there may be no direct correlation between the perceived intensity of pain and the severity of tissue damage.[2]

PAIN VERSUS NOCICEPTION

Pain refers to the conscious, subjective experience or perception of a feeling or sensation, which a person calls pain.[3] Nociception is the physiologic activation of neural pathways by stimuli (noxious, thermal, mechanical, or chemical) that are potentially or currently damaging.[4] A stimulus is deemed nociceptive if it results in a behavioral, withdrawal, or escape response. Proprioception is the awareness of oneself or one's body part relative to their environment. There are many types or descriptions of pain that are descriptive and to some degree may identify sources of ongoing stimulus (**Table 1**).

ANATOMY OF PAIN

In order to understand pain pathways, a brief description of normal anatomy and physiology of the sensory system is required. Afferent sensory nerves send various types of information to the brain. The sensory end organs are made of stimulus accommodating receptors within the skin and tissues (**Fig. 1**). The various receptors are activated by their stimulus to create an electrical impulse or action potential within the sensory nerve. The action potential is transduced to the nerve cell body within the dorsal root ganglion of the spinal cord. The nerves synapse with a spinal cord nerve that carries the action potential signal to the brain through the spinothalamic and spinoparabrachial tracts. The brain network of signal transduction includes synapses within the

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Clin Plastic Surg ■ (2019) ■–■
https://doi.org/10.1016/j.cps.2019.11.001

13. Peripheral and central mechanisms of persistent orofacial pain.

frontiers in Neuroscience

REVIEW
published: 13 November 2019
doi: 10.3389/fnins.2019.01227

Peripheral and Central Mechanisms of Persistent Orofacial Pain

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Neuroplastic changes in the neuronal networks involving the trigeminal ganglion (TG), trigeminal spinal subnucleus caudalis (Vc), and upper cervical spinal cord (C1/C2) are considered the mechanisms underlying the ectopic orofacial hypersensitivity associated with trigeminal nerve injury or orofacial inflammation. It has been reported that peripheral nerve injury causes injury discharges in the TG neurons, and a barrage of action potentials is generated in TG neurons and conveyed to the Vc and C1/C2 after trigeminal nerve injury. Long after trigeminal nerve injury, various molecules are produced in the TG neurons, and these molecules are released from the soma of TG neurons and are transported to the central and peripheral terminals of TG neurons. These changes within the TG cause neuroplastic changes in TG neurons and they become sensitized. The neuronal activity of TG neurons is further accelerated, and Vc and C1/C2 neurons are also sensitized. In addition to this cascade, non-neuronal glial cells are also involved in the enhancement of the neuronal activity of TG, Vc, and C1/C2 neurons. Satellite glial cells and macrophages are activated in the TG after trigeminal nerve injury and orofacial inflammation. Microglial cells and astrocytes are also activated in the Vc and C1/C2 regions. It is considered that functional interaction between non-neuronal cells and neurons in the TG, Vc, and C1/C2 regions is a key mechanism involved in the enhancement of neuronal excitability after nerve injury or inflammation. In this article, the detailed mechanisms underlying ectopic orofacial hyperalgesia associated with trigeminal nerve injury and orofacial inflammation are addressed.

Keywords: orofacial ectopic pain, trigeminal ganglion, trigeminal spinal subnucleus caudalis and upper cervical spinal cord, satellite cell, macrophage, microglia, astrocyte

OPEN ACCESS

Edited by:
Kazutaka Takahashi,
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Reviewed by:
Paul Durham,
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Specialty section:
This article was submitted to Perception Science, a section of the journal Frontiers in Neuroscience

Received: *16 August 2019*
Accepted: *30 October 2019*
Published: *13 November 2019*

Citation:
Shinoda M, Kubo A, Hayashi Y and Iwata K (2019) Peripheral and Central Mechanisms of Persistent Orofacial Pain. Front. Neurosci. 13:1227. doi: 10.3389/fnins.2019.01227

INTRODUCTION

Trigeminal nerve injury and orofacial inflammation are known to frequently cause persistent pain that can spread to adjacent orofacial regions innervated by the uninjured trigeminal nerve branches. Peripheral and central mechanisms are considered to be involved in the persistent ectopic orofacial pain associated with trigeminal nerve injury or orofacial inflammation (Imbe et al., 2001).

Abbreviations: ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CCL2, chemokine C–C motif ligand 2; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; ERK, extracellular signal-regulated kinase; FKN, fractalkine; GFAP, glial fibrillary acidic protein; iNOS, inducible nitric oxide synthase; LIF, leukemia inhibitory factor; MAPK, mitogen-activated protein kinase; Nav, voltage-gated sodium channel; NGF, nerve growth factor; nNOS, neuronal nitric oxide synthase; NOS, nitric oxide synthase; RVM, rostro-ventral medulla; SGC, satellite glial cell; SP, substance P; TG, trigeminal ganglion; TNF, tumor necrosis factor; TNFR, TNF receptor; Vc, trigeminal spinal subnucleus caudalis; Vi, trigeminal subnucleus interpolaris.

14. AMPA receptors and pain – A future therapeutic intervention?

Techniques in Regional Anesthesia and Pain Management (2010) 14, 59-64

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Techniques in
Regional Anesthesia
& Pain Management

AMPA receptors and pain—A future therapeutic intervention?

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AMPA receptors are excitatory glutamate receptors that are critical for synaptic transmission. Not surprisingly, they serve an important function at the synapse between a peripheral nociceptive neuron and a dorsal horn neuron in the spinal cord. Furthermore, a subset of AMPA receptors, calcium permeable AMPA receptors, by allowing calcium influx, is capable of activating calcium-dependent signaling pathways. The activation of these signaling pathways, in turn, leads to long-term changes at the spinal synapses and may even play a role in central sensitization. Several antagonists for AMPA receptors have been developed for preclinical studies of stroke, seizure, amyotropic lateral sclerosis, Alzheimer's disease, addiction, and pain. Many of these agents have shown promise as potential targeted therapeutic interventions for these diseases, and clinical trials are ongoing for many specific AMPA antagonists. In the near future, these AMPA antagonists may emerge as newer analgesics with fewer side effects.

Transmission of neuronal signals, such as the signal of pain, occurs at the synapse between 2 neurons. A presynaptic cell releases a neurotransmitter that binds to a receptor on the postsynaptic cell membrane. The activation of this receptor allows ions, such as Na^+ or Ca^{2+}, into the postsynaptic cell, resulting in a change in the membrane potential. A synapse can be either excitatory or inhibitory, and neurotransmitters can also be excitatory or inhibitory. The most important neurotransmitter of excitatory synapses in the central nervous system (CNS) is glutamate. There are many receptors for glutamate, including kainate, N-methyl-D-aspartate (NMDA), and AMPA receptors (AMPARs). NMDA receptors are known for their role in mediating long-lasting synaptic changes that lead to the formation of memory as well as central sensitization (in pain). AMPARs, structurally similar to NMDA receptors, play an equally important role in synaptic transmission. These receptors, upon binding glutamate, mediate most of the fast excitatory synaptic currents in the CNS. In other words, AMPARs are the receptors that open to depolarize the neuronal membrane sufficiently to fire action potentials. Given their crucial role in mediating synaptic transmission, it is not surprising to find AMPAR malfunction associated with many neurological disorders, including stroke, Alzheimer's disease, amyotropic lateral sclerosis, and addiction. This review examines the structure, electrophysiological properties, and cellular functions of AMPARs, with a focus on the role AMPARs play in the processing of pain signals. We also review the therapeutic potential of modulators of AMPAR as analgesics.

Structure and assembly of AMPARs

AMPARs are transmembrane proteins composed of 4 subunits (tetramers). There are 4 distinct subunits—GluR1-4—in the AMPAR family. Each subunit has about 900 amino acids and 4 main components: a large extracellular amino terminal domain, an adjacent ligand-binding domain,

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1084-208X/$ -see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1053/j.trap.2010.03.004

15. Structure and mechanism of AMPA receptor – auxiliary protein complexes.

Published in final edited form as:
Curr Opin Struct Biol. 2019 February ; 54: 104–111. doi:10.1016/j.sbi.2019.01.011.

Structure and mechanism of AMPA receptor – auxiliary protein complexes

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Abstract

Ionotropic glutamate receptors in vertebrates are composed of three major subtypes – AMPA, kainate and NMDA receptors – and mediate the majority of fast excitatory neurotransmission at chemical synapses of the central nervous system. Among the three major families, native AMPA receptors function as complexes with a variety of auxiliary subunits, which in turn modulate receptor trafficking, gating, pharmacology and permeation. Despite the long history of structure-mechanism studies using soluble receptor domains or intact yet isolated receptors, structures of AMPA receptor-auxiliary subunit complexes have not been available until recent breakthroughs in single-particle cryo-electron microscopy. Single particle cryo-EM studies have, in turn, provided new insights into the structure and organization of AMPA receptor – auxiliary protein complexes and into the molecular mechanisms of AMPA receptor activation and desensitization.

Introduction

In the mammalian brain the majority of fast excitatory neurotransmission is carried out by α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-sensitive ionotropic glutamate receptors located within the post-synaptic density of glutamatergic synapses [1]. AMPA receptors open cation channels in response to binding of glutamate, thus depolarizing post-synaptic membranes. The AMPA receptor signaling complex is typically composed of tetrameric AMPA receptors and a broad range of auxiliary proteins, the latter of which modulate the trafficking, gating, pharmacology and permeation of receptors, leading to spatial and temporal fine-tuning of AMPA receptor function, which in turn is fundamental to synaptic plasticity, learning and memory [2,3].

At present, the group of AMPA receptor auxiliary subunits include transmembrane AMPA receptor regulatory proteins (TARPs) [4], the germ cell-specific gene 1-like protein (GSG1L) [5], cornichon homologs (CNIHs) [6], and the Shisa/cysteine-knot AMPA receptor

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16. Evidence for glutamate as a neuroglial transmitter within sensory ganglia.

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Evidence for Glutamate as a Neuroglial Transmitter within Sensory Ganglia

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Abstract

This study examines key elements of glutamatergic transmission within sensory ganglia of the rat. We show that the soma of primary sensory neurons release glutamate when depolarized. Using acute dissociated mixed neuronal/glia cultures of dorsal root ganglia (DRG) or trigeminal ganglia and a colorimetric assay, we show that when glutamate uptake by satellite glial cells (SGCs) is inhibited, KCl stimulation leads to simultaneous increase of glutamate in the culture medium. With calcium imaging we see that the soma of primary sensory neurons and SGCs respond to AMPA, NMDA, kainate and mGluR agonists, and selective antagonists block this response. Using whole cell patch-clamp technique, inward currents were recorded from small diameter (<30 μm) DRG neurons from intact DRGs (*ex-vivo* whole ganglion preparation) in response to local application of the above glutamate receptor agonists. Following a chronic constriction injury (CCI) of either the inferior orbital nerve or the sciatic nerve, glutamate expression increases in the trigeminal ganglia and DRG respectively. This increase occurs in neurons of all diameters and is present in the somata of neurons with injured axons as well as in somata of neighboring uninjured neurons. These data provides additional evidence that glutamate can be released within the sensory ganglion, and that the somata of primary sensory neurons as well as SGCs express functional glutamate receptors at their surface. These findings, together with our previous gene knockdown data, suggest that glutamatergic transmission within the ganglion could impact nociceptive threshold.

Citation: Kung L-H, Gong K, Adedoyin M, Ng J, Bhargava A, et al. (2013) Evidence for Glutamate as a Neuroglial Transmitter within Sensory Ganglia. PLoS ONE 8(7): e68312. doi:10.1371/journal.pone.0068312

Editor: Alexander Binshtok, The Hebrew University Medical School, Israel

Received February 1, 2013; **Accepted** May 28, 2013; **Published** July 2, 2013

Funding: Supported by NIH NS061241, NS051336 and the Painless Research Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Glutamate is the common excitatory neurotransmitter of the central and peripheral nervous systems and is found in both nociceptive as well as non-nociceptive sensory pathways [1,2,3,4]. The ubiquitous distribution of glutamate has made it difficult to formulate strategies that could target glutamatergic transmission involved in a specific function such as nociception while leaving other processes intact. Thus the possibility of targeting glutamatergic transmission in the peripheral nervous system has been suggested given that small diameter primary sensory neurons, many of which are nociceptive, express glutamate and glutamate receptors [5,6,7]. Activation of these neurons leads to glutamate release at their central as well as peripheral terminals [8,9,10], and nociception [11,12].

The possibility that glutamate is also released within the sensory ganglion is contentious as there are no synapses on the soma of primary sensory neurons. Clearly, the cell membranes of primary sensory neuron somas contain ionotropic (iGluR) and metabotropic (mGluR) receptors [13,14,15,16]. Moreover, the machinery for production, release, and recycling of glutamate is present in sensory ganglia including the amidohydrolase enzyme, glutaminase [17,18], vesicular glutamate transporters (VGLUT1, 2 and 3) [19,20], the glutamate aspartate transporter (GLAST) and glutamate transporter 1 (GLT1) [21], as well as the recycling enzyme glutamine synthetase [17,22]. This, and the presence of glutamate within the soma would allow for local non-synaptic glutamatergic transmission. We have indirect evidence for non-synaptic transmission from experiments in the trigeminal ganglion in which a glutamate-glutamine cycle enzyme or a glutamate uptake transporter were knocked-down using double stranded RNA [22,23]. These studies showed that the knockdown was confined to the local satellite glial cells (SGCs) and that pain behavior was consistently altered, which can be best explained by a change in intraganglionic glutamatergic transmission.

The goal of the present study was to determine if glutamate is released by the soma of primary sensory neurons and if functional glutamate receptors are present at the surface of the soma of these neurons. It has generally assumed that glutamate vesicles and receptor proteins found in the soma of primary sensory neurons are destined for transport to axon terminals and that functional glutamate receptors are not inserted onto the somatic membrane. Evidence from *in vitro* studies, however, suggests that the soma of primary sensory neurons can release glutamate [24,25,26] and express functional NMDA receptors at the surface [27], supporting the presence of intraganglionic glutamatergic transmission [1]. There is precedence for non-synaptic release of other neurotransmitters and neuromodulators within sensory ganglia. Examples are

17. The role of AMPA receptors in postsynaptic mechanisms of synaptic plasticity.

frontiers in
CELLULAR NEUROSCIENCE

REVIEW ARTICLE
published: 27 November 2014
doi: 10.3389/fncel.2014.00401

The role of AMPA receptors in postsynaptic mechanisms of synaptic plasticity

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In the mammalian central nervous system, excitatory glutamatergic synapses harness neurotransmission that is mediated by ion flow through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). AMPARs, which are enriched in the postsynaptic membrane on dendritic spines, are highly dynamic, and shuttle in and out of synapses in an activity-dependent manner. Changes in their number, subunit composition, phosphorylation state, and accessory proteins can all regulate AMPARs and thus modify synaptic strength and support cellular forms of learning. Furthermore, dysregulation of AMPAR plasticity has been implicated in various pathological states and has important consequences for mental health. Here we focus on the mechanisms that control AMPAR plasticity, drawing particularly from the extensive studies on hippocampal synapses, and highlight recent advances in the field along with considerations for future directions.

Keywords: AMPAR, homeostatic plasticity, Hebbian plasticity, synaptic plasticity, synaptic transmission, trafficking

INTRODUCTION

The birth of modern neuroscience arguably started with the seminal work of Cajal (1852–1934, Doyle, 1939) who identified neurons as individual units embedded within the vastly complex network of brain tissue. However, little was known about how these intricate and beautiful cells communicated with each other until the advent of more sophisticated techniques that allowed probing of the communication across the synaptic cleft. Studies at the neuromuscular junction, an experimental preparation that was more accessible than the brain, demonstrated that postsynaptic receptors were largely stable and were generally unresponsive to changes in activity level (Fambrough and Hartzell, 1972; Sanes and Lichtman, 1999). Whether this applied to the central nervous system was begun to be answered in the 1970s and 80s, when Bliss and Lømo, working in rabbit hippocampus, first demonstrated that a stimulus could cause an increase in synaptic strength that was long lasting, termed long-term potentiation (LTP: Bliss and Lømo, 1973). The discovery of LTP set in motion the background for the flurry of studies aimed to test if memories are stored at subsets of synapses distributed throughout neuronal networks, and if changes in these tiny structures underlie the ability to learn new behaviors. A particular class of glutamatergic receptors, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs: Beneyto and Meador-Woodruff, 2004), is a key determinant of synaptic strength, and the plasticity of AMPARs is the focus of this review. This is a large field that has spanned over three decades now, and its progress has relied on diverse experimental approaches using *in vitro* and *in vivo* preparations, from biochemistry, cell biology, electrophysiology, to state-of-the-art imaging combined with increasingly sophisticated genetic manipulation.

After a brief introduction to the discovery and history of AMPARs, this review focuses on their role in postsynaptic plasticity in the hippocampus and the recent advances over the last few years. How do AMPARs initially get to the cell surface, and once there, how are they targeted to and retained at synapses? Neighboring synapses sharing the same dendrite may experience significantly different activity levels, and this impacts AMPAR mobility and synaptic retention. Furthermore, AMPAR subunits are differentially regulated by neuronal activity, especially with respect to enzyme-mediated phosphorylation/dephosphorylation cycles that drive their insertion or removal from the synapse. The incorporation of calcium-permeable AMPARs into synapses in response to stimuli is also an important modulation. Neurons are capable of a variety of plastic changes, and synapse strength is both regulated locally and across thousands of synapses cell-wide. How are AMPARs differentially regulated by these separate forms of plasticity? Finally we will discuss changes in AMPAR plasticity in age-related cognitive decline and brain pathologies, and the implications for normal neuronal function.

WHAT ARE AMPARs?

AMPARs are tetrameric, cation-permeable ionotropic glutamate receptors, and are expressed throughout the brain (Beneyto and Meador-Woodruff, 2004). The four AMPAR subunits (GluA1–GluA4) are encoded by the genes GRIA1-GRIA4, and are assembled as dimers-of-dimers to form the hetero-tetrameric receptors (Hollmann and Heinemann, 1994; Traynelis et al., 2010), although homo-tetrameric receptors have been reported (Wenthold et al., 1996; Lu et al., 2009). Upon binding of glutamate, the pore opening allows the influx of Na^+ ions (along with K^+ efflux) to depolarize the postsynaptic compartment; however, depending on the subunit composition and the RNA

18. The AMPA receptor code of synaptic plasticity.

Published in final edited form as:
Neuron. 2018 October 24; 100(2): 314–329. doi:10.1016/j.neuron.2018.10.018.

The AMPA receptor code of synaptic plasticity

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Abstract

Changes in the properties and post-synaptic abundance of AMPA-type glutamate receptors (AMPARs) are major mechanisms underlying various forms of synaptic plasticity, including long-term potentiation (LTP), long-term depression (LTD), and homeostatic scaling. The function and the trafficking of AMPARs to and from synapses is modulated by specific AMPAR GluA1-4 subunits, subunit specific protein interactors, auxiliary subunits, and post-translational modifications. Layers of regulation are added to AMPAR tetramers through these different interactions and modifications, increasing the computational power of synapses. Here we review the reliance of synaptic plasticity on AMPAR variants and propose "the AMPAR code" as a conceptual framework. The AMPAR code suggests that AMPAR variants will be predictive of the types and extent of synaptic plasticity which can occur and that a hierarchy exists such that certain AMPARs will be disproportionally recruited to synapses during LTP/homeostatic scaling-up, or removed during LTD/homeostatic scaling-down.

Introduction

Synapses in the central nervous system undergo bidirectional changes in synaptic strength, a process referred to as synaptic plasticity. These changes occur locally at individual synapses, during long-term potentiation (LTP) or long-term depression (LTD), collectively referred to as Hebbian plasticity, or globally during homeostatic scaling (Huganir and Nicoll, 2013, Turrigiano, 2008). It is widely believed that changes in synaptic strength through Hebbian plasticity form the cellular basis of learning and memory, while homeostatic scaling is an important mechanism for bidirectional regulation of neuronal excitability and for maintaining synaptic strength within a dynamic range. A primary mechanism in the control of synaptic strength during plasticity is an alteration in the number, composition and

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19. AMPA receptors and pain – A future therapeutic intervention?

Techniques in Regional Anesthesia and Pain Management (2010) 14, 59-64

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Techniques in
Regional Anesthesia
& Pain Management

AMPA receptors and pain—A future therapeutic intervention?

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Transmission of neuronal signals, such as the signal of pain, occurs at the synapse between 2 neurons. A presynaptic cell releases a neurotransmitter that binds to a receptor on the postsynaptic cell membrane. The activation of this receptor allows ions, such as Na^+ or Ca^{2+}, into the postsynaptic cell, resulting in a change in the membrane potential. A synapse can be either excitatory or inhibitory, and neurotransmitters can also be excitatory or inhibitory. The most important neurotransmitter of excitatory synapses in the central nervous system (CNS) is glutamate. There are many receptors for glutamate, including kainate, N-methyl-D-aspartate (NMDA), and AMPA receptors (AMPARs). NMDA receptors are known for their role in mediating long-lasting synaptic changes that lead to the formation of memory as well as central sensitization (in pain). AMPARs, structurally similar to NMDA receptors, play an equally important role in synaptic transmission. These receptors, upon binding glutamate, mediate most of the fast excitatory synaptic currents in the CNS. In other words, AMPARs are the receptors that open to depolarize the neuronal membrane sufficiently to fire action potentials. Given their crucial role in mediating synaptic transmission, it is not surprising to find AMPAR malfunction associated with many neurological disorders, including stroke, Alzheimer's disease, amyotropic lateral sclerosis, and addiction. This review examines the structure, electrophysiological properties, and cellular functions of AMPARs, with a focus on the role AMPARs play in the processing of pain signals. We also review the therapeutic potential of modulators of AMPAR as analgesics.

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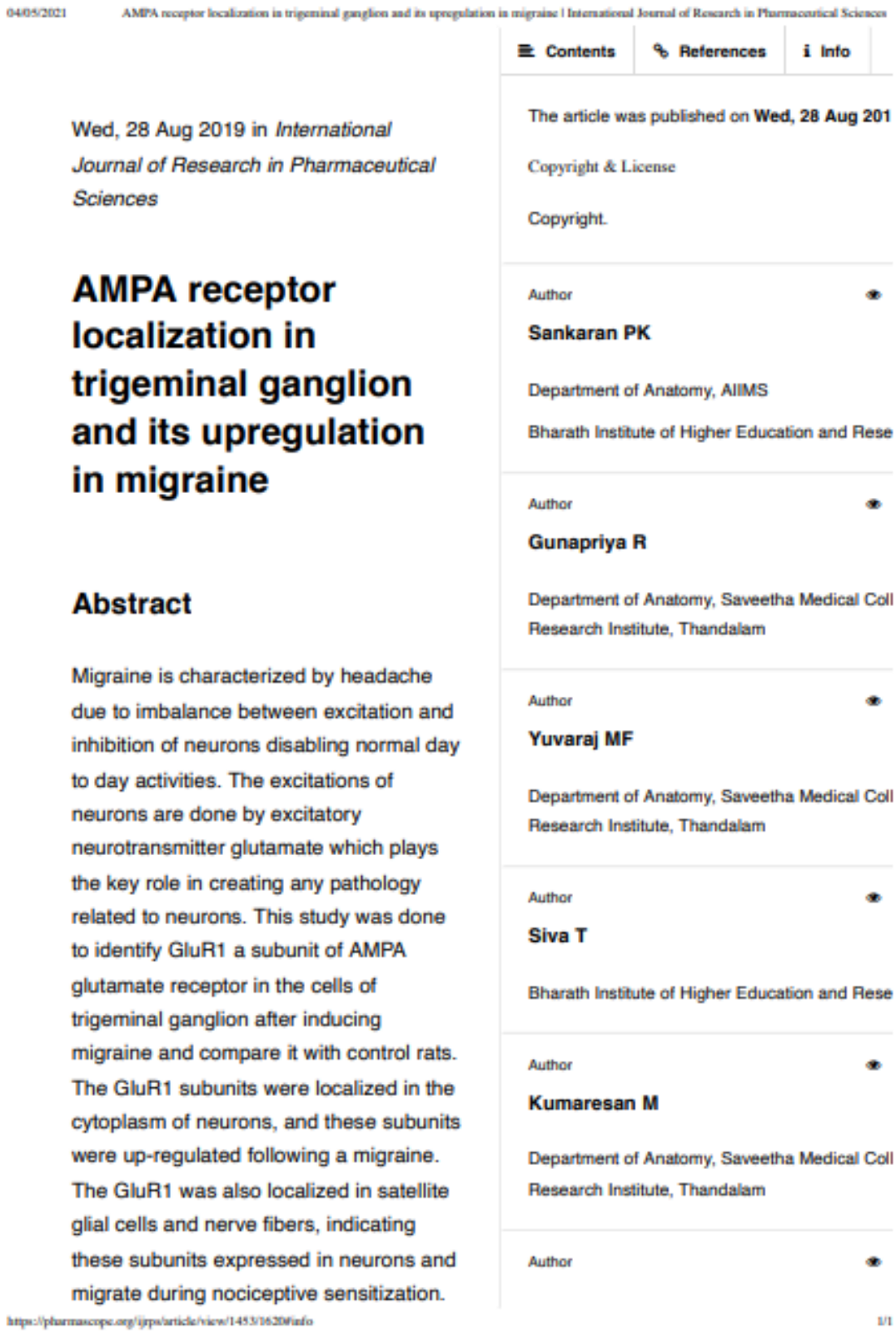
doi:10.1053/j.trap.2010.03.004

Structure and assembly of AMPARs

AMPARs are transmembrane proteins composed of 4 subunits (tetramers). There are 4 distinct subunits—GluR1-4—in the AMPAR family. Each subunit has about 900 amino acids and 4 main components: a large extracellular amino terminal domain, an adjacent ligand-binding domain,

20. AMPA receptor localization in trigeminal ganglion and its upregulation in migraine.



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Wed, 28 Aug 2019 in *International Journal of Research in Pharmaceutical Sciences*

AMPA receptor localization in trigeminal ganglion and its upregulation in migraine

Abstract

Migraine is characterized by headache due to imbalance between excitation and inhibition of neurons disabling normal day to day activities. The excitations of neurons are done by excitatory neurotransmitter glutamate which plays the key role in creating any pathology related to neurons. This study was done to identify GluR1 a subunit of AMPA glutamate receptor in the cells of trigeminal ganglion after inducing migraine and compare it with control rats. The GluR1 subunits were localized in the cytoplasm of neurons, and these subunits were up-regulated following a migraine. The GluR1 was also localized in satellite glial cells and nerve fibers, indicating these subunits expressed in neurons and migrate during nociceptive sensitization.

The article was published on **Wed, 28 Aug 201**

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https://pharmascope.org/ijrps/article/view/1453/16208/info 1/1

21. Peripheral AMPA receptors contribute to muscle nociception and c-fos activation.

Published in final edited form as:
Neurosci Res. 2008 October ; 62(2): 97–104. doi:10.1016/j.neures.2008.06.007.

Peripheral AMPA receptors contribute to muscle nociception and *c-fos* activation

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Abstract

In this study, involvement of peripheral AMPA receptors in mediating craniofacial muscle pain was investigated. AMPA receptor subunits, GluR1 and GluR2, were predominantly expressed in small to medium size neurons but more GluR2 positive labeling were encountered in trigeminal ganglia (TG) of male Sprague Dawley rats. A greater prevalence of GluR2 is reflected by the significantly higher percentage of GluR2 than GluR1 positive masseter afferents. Nocifensive behavior and *c-fos* immunoreactivity were assessed from the same animals that received intramuscular mustard oil (MO) with or without NBQX, a potent AMPA/KA receptor antagonist. Masseteric MO produced nocifensive hindpaw shaking responses that peaked in the first 30 seconds and gradually diminished over a few minutes. There was a significant difference in both peak and overall MO-induced nocifensive responses between NBQX and vehicle pre-treated rats. Subsequent Fos studies also showed that peripheral NBQX pre-treatment effectively reduced the MO-induced neuronal activation in the subnucleus caudalis of the trigeminal nerve (Vc). These combined results provide compelling evidence that acute muscle nociception is mediated, in part, by peripherally located AMPA/KA receptors, and that blockade of multiple peripheral glutamate receptor subtypes may provide a more effective means of reducing muscular pain and central neuronal activation.

Keywords

Muscle pain; mustard oil; peripheral glutamate receptors; masseter

1. INTRODUCTION

Glutamate receptors located on peripheral terminals of nociceptors are activated by glutamate released from various sources such as neurons, Schwan cells, and macrophages, following injury or inflammation (Piani et al., 1991; Parpura et al., 1995; deGroot et al., 2000; Lawand et al., 2000). Glutamate administered directly to the masseter muscle activates and sensitizes nociceptors in rats and produces pain in human subjects via peripheral NMDA receptors

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22. Neural pathways of craniofacial muscle pain: Implications for novel treatments.

Critical Reviews in Oral Biology & Medicine

Neural Pathways of Craniofacial Muscle Pain: Implications for Novel Treatments

Journal of Dental Research
2020, Vol. 99(9) 1004–1012

DOI: 10.1177/0022034520919384
journals.sagepub.com/home/jdr

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Abstract

Craniofacial muscle pain is highly prevalent in temporomandibular disorders but is difficult to treat. Enhanced understanding of neurobiology unique to craniofacial muscle pain should lead to the development of novel mechanism-based treatments. Herein, we review recent studies to summarize neural pathways of craniofacial muscle pain. Nociceptive afferents in craniofacial muscles are predominantly peptidergic afferents enriched with TRPV1. Signals from peripheral glutamate receptors converge onto TRPV1, leading to mechanical hyperalgesia. Further studies are needed to clarify whether hyperalgesic priming in nonpeptidergic afferents or repeated acid injections also affect craniofacial muscle pain. Within trigeminal ganglia, afferents innervating craniofacial muscles interact with surrounding satellite glia, which enhances the sensitivity of the inflamed neurons as well as nearby uninjured afferents, resulting in hyperalgesia and ectopic pain originating from adjacent orofacial tissues. Craniofacial muscle afferents project to a wide area within the trigeminal nucleus complex, and central sensitization of medullary dorsal horn neurons is a critical factor in muscle hyperalgesia related to ectopic pain and emotional stress. Second-order neurons project rostrally to pathways associated with affective pain, such as parabrachial nucleus and medial thalamic nucleus, as well as sensory-discriminative pain, such as ventral posteromedial thalamic nuclei. Abnormal endogenous pain modulation can also contribute to chronic muscle pain. Descending serotonergic circuits from the rostral ventromedial medulla facilitate activation of second-order neurons in the trigeminal nucleus complex, which leads to the maintenance of mechanical hyperalgesia of inflamed masseter muscle. Patients with temporomandibular disorders exhibit altered brain networks in widespread cortical and subcortical regions. Recent development of methods for neural circuit manipulation allows silencing of specific hyperactive neural circuits. Chemogenetic silencing of TRPV1-expressing afferents or rostral ventromedial medulla neurons attenuates hyperalgesia during masseter inflammation. It is likely, therefore, that further delineation of neural circuits mediating craniofacial muscle hyperalgesia potentially enhances treatment of chronic muscle pain conditions.

Keywords: temporomandibular disorder, orofacial muscle pain, primary afferents, trigeminal ganglia, descending pain modulation, chemogenetics

Introduction

Craniofacial muscle pain is associated with substantial morbidity and affects individuals through different conditions. Acute conditions, such as space abscesses, can cause muscle pain. Tension-type headaches are also likely to involve pericranial muscle pain. Temporomandibular disorders (TMDs) are the most prevalent conditions involving craniofacial muscle pain. In diagnostic criteria for TMD, masticatory muscle disorders include myalgia, tendonitis, myositis, and spasm (Schiffman et al. 2014). Myalgia is defined as "pain of muscle origin that is affected by jaw movement, function, or parafunction, and replication of this pain occurs with provocation testing of the masticatory muscles." Since TMD occurrence is influenced by multiple factors, including jaw parafunction, psychosocial conditions, and genetic factors, it is important to understand in detail the peripheral and central neurobiological mechanisms underlying pain from the jaw muscles.

Recent studies suggest that the craniofacial system and the spinal system show distinct peripheral and central pain processing or different sensitivities. Acute inflammation induced by carrageenan produces greater and longer pressure-induced mechanical hyperalgesia in the masseter muscle than in the gastrocnemius muscle (Bagues et al. 2017). Trigeminal nociceptors uniquely contain a subset of afferents that bypass second-order neurons in the medullary dorsal horn and directly project to the parabrachial nucleus (PBN), which may enhance affective pain (Rodriguez et al. 2017). Furthermore, a calcitonin gene-related peptide (CGRP) receptor antagonist attenuates orofacial neuropathic pain but not spinal neuropathic pain (Michot et al. 2012). Therefore, the mechanisms of craniofacial pain are unique and cannot be considered identical to those of spinal pain.

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23. Alterations in the masticatory system in patients with amyotrophic lateral sclerosis.

Alterations in the Masticatory System in Patients with Amyotrophic Lateral Sclerosis

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Aims: To determine the effect of amyotrophic lateral sclerosis (ALS) on aspects of masticatory function and to assess the relationship between ALS and the prevalence of traumatic mucosal lesions caused by oral self-injury. **Methods:** A total of 153 ALS patients and 23 control subjects participated in this cross-sectional study. Clinical characteristics including site of onset, medication, type of feeding, and use of noninvasive mechanical ventilation were recorded. The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) protocol and a specific questionnaire to assess aspects of masticatory dysfunction and frequency of self-injury of the oral mucosa were applied to all participants. Maximum mandibular range of motion, maximum bite force, and maximum finger-thumb grip force were determined and tested with Mann Whitney, Kruskal-Wallis, or chi-square tests. $P < .05$ was considered significant. **Results:** Maximum unassisted and assisted mouth opening, protrusion, left laterotrusion, and finger-thumb grip force were significantly reduced in both spinal- (n = 102) and bulbar-onset (n = 40) patients compared to the control group; however, bite force was reduced only in bulbar-onset patients. ALS patients with tube feeding (n = 16) had the greatest reduction in maximum bite force and mandibular opening. There was no relationship between TMD and ALS. Oral self-injury due to biting was more frequent in the ALS group (29.9%) than in the control group (8.7%) and in the bulbar-onset group (55.0%) compared to the spinal- (20.8%) and respiratory-onset (18.2%) groups. Of the ALS patients in the study, 10% sought dental treatment related to the condition. **Conclusion:** The ALS patients in this study had a reduction in finger-thumb grip force that was twice as great as the reduction in bite force. The maximum range of mandibular movement was also reduced, especially in bulbar-onset patients. ALS patients did not have a higher prevalence of TMD but did have more traumatic mucosal injury than controls. The dentist should be an integral part of the multidisciplinary team to manage ALS patients.
J Oral Facial Pain Headache 2018;32:84–90. doi: 10.11607/ofph.1882

Keywords: *amyotrophic lateral sclerosis, craniomandibular disorders, mandibular range of motion, occlusal force, self-biting*

Amyotrophic lateral sclerosis (ALS) is a heterogenous, multisystem, progressive neurodegenerative disease that affects the lower and upper motor neurons in the spinal cord, brainstem, and brain, causing muscle atrophy, muscle weakness, and spasticity.[1] Risk factors associated with ALS are older age, male sex, and family history.[2] Its incidence rates in Catalonia and Europe are approximately 1.4 and 2.1 per 100,000 people a year, respectively,[3,4] and survival rates vary from months to several years, with median survival time from onset ranging from 24 months in northern Europe to 48 months in central Asia.[5]

The typical clinical characteristics of ALS are variable and depend on whether the site of onset is spinal, bulbar, or respiratory. Most patients with ALS have a spinal onset, causing referred weakness and muscle atrophy, fasciculations (reflecting involvement of lower motor neurons), and hyperreflexia and hypertonia (reflecting involvement of upper motor neurons). Weakness starts in bulbar muscles in about 20% of patients, with dysarthria, dysphagia, and tongue fasciculations. Bulbar-onset ALS has a poorer prognosis due to swallowing difficulties, weight loss, aspiration, and respiratory involvement, with poorer

24. Masticatory muscle pain and progressive mouth opening limitation caused by amyotrophic lateral sclerosis.

Masticatory Muscle Pain and Progressive Mouth Opening Limitation Caused by Amyotrophic Lateral Sclerosis: A Case Report

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This article reports a case of masticatory muscle pain and progressive limited mouth opening secondary to amyotrophic lateral sclerosis (ALS), popularly known as Lou Gehrig's disease. The symptoms were first mistaken as those of temporomandibular disorders, before fatty degeneration of all masticatory muscles were discovered on magnetic resonance imaging (MRI). ALS should be considered in the differential diagnosis process when the patient presents with longstanding progressive mouth opening limitation associated with pain. MRI could facilitate the diagnostic process. *J Oral Facial Pain Headache 2015;29:91–96. doi: 10.11607/ofph.1340*

Key words: *amyotrophic lateral sclerosis, motor neuron disease, mouth opening limitation, orofacial pain*

Amyotrophic lateral sclerosis (ALS), which is also known as Lou Gehrig's disease, is the most common adult-onset motor neuron disease. The disease shows selective and progressive degeneration of motor neurons, which results in spasticity, hyperexcitability, and appearance of pathologic reflexes caused by degeneration of upper motor neurons of the cerebral cortex, as well as muscle weakness and atrophy followed by progressive paralysis caused by the degeneration of lower motor neurons of the brainstem and anterior horn of the spinal cord.[1,2] Incidence rates are relatively low in the general population, being 1.5 to 2.5 per 1,000,000 persons per year.[3] The consequences of the progressive degeneration of motor neurons that innervate voluntary muscles are generally fatal, since respiratory failure usually eventuates and results in death. The average median survival is 19 months from diagnosis and 30 months from onset.[4] The etiology of ALS is yet to be elucidated, but accumulated evidence suggests that, similar to other chronic neurodegenerative diseases, ALS is a complex genetic disorder with different subtypes according to genetic mutations and their interaction with environmental risk factors.

In the following case, the patient was initially mistaken as presenting features indicative of temporomandibular disorders (TMD) due to the patient's masticatory muscle pain and limitations of mouth opening. However, the severity and duration of the limited mouth opening raised the need for further imaging.

Case Report

A 48-year-old male patient visited the Orofacial Pain Clinic, Department of Oral Medicine and Oral Diagnosis, Seoul National University Dental Hospital with the chief complaint of stiffness of both masseter muscles during function and progressive limitations of mouth opening that recently seemed to be getting worse. The decreased mouth opening range had first been noticed 5 years earlier. The patient reported a history of open lock after maximum mouth opening and that diffuse pain had appeared in the shoulder, low back, and thigh area. Such systemic pain had recently progressed to have an intermittent electrical aspect.

25. AMPA receptor GluA1 Ser831 phosphorylation is critical for nitroglycerin-induced migraine-like pain.

HHS Public Access
Author manuscript
Neuropharmacology. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:
Neuropharmacology. 2018 May 01; 133: 462–469. doi:10.1016/j.neuropharm.2018.02.026.

AMPA receptor GluA1 Ser831 phosphorylation is critical for nitroglycerin-induced migraine-like pain

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Abstract

Migraine is the third most common disease worldwide; however, the mechanisms underlying migraine headache are still not fully understood. Previous studies have demonstrated that α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor phosphorylation plays an important role in central sensitization of pain transmission. In the present study, we observed that AMPA receptor GluA1 Ser831 phosphorylation was enhanced in the spinal trigeminal nucleus caudalis (Sp5C) after intraperitoneal injection of nitroglycerin (NTG). The NTG injection induced acute migraine-like pain including photophobia and mechanical hypersensitivity as reported previously. Interestingly, targeted mutation of GluA1 Ser831 site to prevent phosphorylation significantly inhibited NTG-induced migraine-like pain. Moreover, NTG incubation caused a robust Ca^{2+} influx in cultured brainstem neurons, which was dramatically inhibited by GluA1 S831A (serine at the 831 site of GluA1 is mutated to alanine) phospho-deficient mutation, and treatment with 1-naphthyl acetyl spermine (NASPM), a selective Ca^{2+}-permeable AMPA receptor channel blocker, dose-dependently blocked the NTG-evoked increase of Ca^{2+} influx in the cultured neurons. We further found that intra-Sp5C injection of NASPM significantly inhibited NTG-produced mechanical hypersensitivity. These results suggest that AMPA receptor phosphorylation at the Ser831 site in the Sp5C is critical for NTG-induced migraine-like pain.

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Potential Conflicts of Interest: The authors have no conflicts of interest to declare.

26. Involvement of AMPA receptor Glur2 and Glur3 trafficking in trigeminal spinal subnucleus caudalis and C1/C2 neurons in acute-facial inflammatory pain.

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Involvement of AMPA Receptor GluR2 and GluR3 Trafficking in Trigeminal Spinal Subnucleus Caudalis and C1/C2 Neurons in Acute-Facial Inflammatory Pain

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Abstract

To evaluate the involvement of trafficking of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) GluR2 and GluR3 subunits in an acute inflammatory orofacial pain, we analyzed nocifensive behavior, phosphorylated extracellular signal-regulated kinase (pERK) and Fos expression in Vi/Vc, Vc and C1/C2 in GluR2 delta7 knock-in (KI), GluR3 delta7 KI mice and wild-type mice. We also studied Vc neuronal activity to address the hypothesis that trafficking of GluR2 and GluR3 subunits plays an important role in Vi/Vc, Vc and C1/C2 neuronal activity associated with orofacial inflammation in these mice. Late nocifensive behavior was significantly depressed in GluR2 delta7 KI and GluR3 delta7 KI mice. In addition, the number of pERK-immunoreactive (IR) cells was significantly decreased bilaterally in the Vi/Vc, Vc and C1/C2 in GluR2 delta7 KI and GluR3 delta7 KI mice compared to wild-type mice at 40 min after formalin injection, and was also significantly smaller in GluR3 delta7 KI compared to GluR2 delta7 KI mice. The number of Fos protein-IR cells in the ipsilateral Vi/Vc, Vc and C1/C2 was also significantly smaller in GluR2 delta7 KI and GluR3 delta7 KI mice compared to wild-type mice 40 min after formalin injection. Nociceptive neurons functionally identified as wide dynamic range neurons in the Vc, where pERK- and Fos protein-IR cell expression was prominent, showed significantly lower spontaneous activity in GluR2 delta7 KI and GluR3 delta7 KI mice than wild-type mice following formalin injection. These findings suggest that GluR2 and GluR3 trafficking is involved in the enhancement of Vi/Vc, Vc and C1/C2 nociceptive neuronal excitabilities at 16–60 min following formalin injection, resulting in orofacial inflammatory pain.

Citation: Miyamoto M, Tsuboi Y, Honda K, Kobayashi M, Takamiya K, et al. (2012) Involvement of AMPA Receptor GluR2 and GluR3 Trafficking in Trigeminal Spinal Subnucleus Caudalis and C1/C2 Neurons in Acute-Facial Inflammatory Pain. PLoS ONE 7(8): e44055. doi:10.1371/journal.pone.0044055

Editor: Alice Y. W. Chang, Kaohsiung Chang Gung Memorial Hospital, Taiwan

Received December 26, 2011; **Accepted** July 30, 2012; **Published** August 24, 2012

Funding: This study was supported in part by Research Grants from Sato and Uemura Funds from Nihon University School of Dentistry, and a grant from the Dental Research Center, Nihon University School of Dentistry; a Nihon University multidisciplinary research grant for KI; grants from the Ministry of Education, Culture, Sports, Science, and Technology to promote the multidisciplinary research project "Translational Research Network on Orofacial Neurological Disorders" at Nihon University School of Dentistry; Japan-Canada (CIHR) Joint Health Research Program, and National Institutes of Health grant DE015420. No additional external funding received for this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

The alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) consists of a hetero-tetrametric combination of 4 receptor subunits, GluR1-4 [1], and is known to exert its actions as complexes of subunits, mainly GluR1/2 and GluR2/3 [2]. GluRs1-4 are highly expressed in the spinal dorsal horn (DH), and are thought to be involved in somatosensory processing [3]. In an animal peripheral inflammatory pain model, the N-ethylmaleimide-sensitive fusion protein (NSF) was reported to be involved in central sensitization of spinal cord neurons through a GluR2 subunit composition switch following peripheral inflammation [4]. It has also been reported that interactions between the GluR2 C-terminus and its binding proteins regulate receptor internalization in spinal DH neurons in an inflammatory pain model [5]. Phosphorylation of the GluR2 C-terminus by protein kinase C (PKC) regulates these protein bindings. GluR2 is also known to be internalized via NMDA receptor-triggered PKC activation in DH neurons following persistent inflammation of the hind paw [5,6]. Sequential studies using AMPAR subunit knockout (KO) mice have also shown that GluR2 enhances nociceptive plasticity, resulting in the enhancement of inflammatory hyperalgesia, whereas GluR1 KO mice show subtle abnormalities in the inflammatory pain [7,8]. This indicates that the GluR2 subunit

27. How to erase memory traces of pain and fear.

Review

How to erase memory traces of pain and fear

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Pain and fear are both aversive experiences that strongly impact on behaviour and well being. They are considered protective when they lead to meaningful, adaptive behaviour such as the avoidance of situations that are potentially dangerous to the integrity of tissue (pain) or the individual (fear). Pain and fear may, however, become maladaptive if expressed under inappropriate conditions or at excessive intensities for extended durations. Currently emerging concepts of maladaptive pain and fear suggest that basic neuronal mechanisms of memory formation are relevant for the development of pathological forms of pain and fear. Thus, the processes of erasing memory traces of pain and fear may constitute promising targets for future therapies.

Memory traces of pain and fear

Memory traces of pain and fear are encoded by distinct but partially overlapping sets of synapses. For example, painful stimuli are highly effective for inducing fear learning [1]. Indeed, electric foot shock is the most commonly used outcome for fear-memory studies and it remains untested whether the mechanisms and principles outlined below apply equally to fear memories that do not involve activation of nociceptive pathways. However, acute and chronic pain are often associated with fear or anxiety [2–5]. Brain areas associated with fear, such as the amygdala and the cingulate and medial prefrontal cortices [6–8], are also relevant for the emotional/aversive and cognitive aspects of pain [9–12]. Here, we focus on forms of chronic pain and fear that involve the staged formation of enduring synaptic plasticity (Box 1). We discuss recent findings suggesting that some memory traces of pain and fear can be erased, which may provide novel options for future treatments.

Memory traces of pain

Numerous clinically relevant conditions may change the properties and functions of the nociceptive system in ways that lead to: (i) the amplification of pain and the lowering of pain thresholds (hyperalgesia); (ii) spontaneous pain; (iii) spreading pain; and/or (iv) pain elicited by touch fibres (mechanical allodynia) (see Box 2 for definitions). Common causes include acute painful events (e.g., surgery, trauma, inflammation), drugs (e.g., opioids, chemotherapeutics), and diseases such as neuropathies, type I and type II diabetes, fibromyalgia, and sickness syndrome. The duration of pathological pain may exceed the duration of its primary cause by days to years and may involve synaptic plasticity at various sites in the nociceptive network (Box 3).

At present, only a few studies have specifically addressed the question of whether memory traces of pain can be erased under clinical conditions, but some treatments do appear to have lasting effects. Some forms of counter stimulation – such as transcutaneous electrical nerve stimulation, (electro-)acupuncture, and some forms of physical therapy – are reported to have analgesic effects that outlast the period of treatment in selected patients [13,14], but counterexamples exist, as described in [15,16].

Induction, consolidation, and maintenance phases of lasting pain

Induction phase. Strong and/or lasting noxious stimuli trigger various neuroplastic changes in the central nervous system (CNS) including activity-dependent long-term potentiation (LTP) at the first synaptic relays in nociceptive pathways [17]. Paradoxically, similar 'memory traces of pain' can evolve in the absence of any noxious stimuli. For example, hyperalgesia and synaptic facilitation may develop during continuous application of opioids or on their abrupt withdrawal (opioid-induced hyperalgesia) [18–20] without the need for any concomitant stimulation of nociceptive nerve fibres.

Consolidation phase. The development of chronic pain is an active process that requires time and which can be interrupted. The consolidation phase may last for hours to weeks. Some elements that are required for the consolidation of LTP in nociceptive pathways are shown in Figure 1A. Therapeutic interference within the consolidation process may fully prevent the development of lasting (e.g., neuropathic) pain. For example, when neuropathic pain is induced in rats by placing a cuff around the sciatic nerve, mechanical hyperalgesia develops within 24 h. Removal of the cuff 24 h but not 4 days after implantation allows full recovery of mechanical thresholds within 18 days [21]. Likewise, a single intrathecal injection of GABA apparently reverses neuropathic pain permanently when given 1 week after a chronic constriction injury of the sciatic nerve in rats, but not when given more than 2–3 weeks after the injury [22].

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0166-2236/$ – see front matter
 http://dx.doi.org/10.1016/j.tins.2013.03.004