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Facial pain : from animal models to functional neuroimaging studies

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Abstract

This paper summarizes some recent findings on the physiopathology of facial pain. Over the past decade, a number of animal models of facial pain have been developed. Two of these models are discussed in more detail. The model developed by Strassman and Burstein has provided a useful tool for the study of the mechanisms underlying migraine. Single unit recordings revealed that medullary dorsal horn neurons show a long-lasting increased response to dural and cutaneous periorbital mechanical and thermal stimulation after application of inflammatory agents to the dura. In addition, dural and cutaneous receptive fields largely expanded and spontaneous ongoing activity developed. These findings suggest that the extracranial hypersensitivity that is often observed in headache may have an intracranial origin. The second model that is discussed is the model of facial neuropathic pain after infraorbital nerve ligation developed by Vos and colleagues. In contrast to the previous model which is an acute electrophysiological preparation, the infraorbital nerve model is a behavioural model. It can therefore be used both for electrophysiological and behavioural studies. In recent years, a number of functional neuroimaging studies of facial pain appeared. Studies performed in cluster headache patients seem to point to a crucial role of the hypothalamus in this syndrome. However, since hypothalamic activation has also been reported in some other types of (facial) pain, the specificity of the role of the hypothalamus in cluster headache remains to be proven.

Key words : Animal models ; facial pain ; migraine ; cluster headache ; PET ; hypothalamus

Introduction

In the 1930's, Wolff and colleagues proposed their theory on the vasogenic origin of migraine. This theory was based on a number of observations. First, in many migraine patients, extracranial blood vessels become dilated during a migraine attack. Second, Penfield and colleagues showed that stimulation of the intracranial vessels causes headache in conscious patients. Third, substances that vasoconstrict vessels abolish the headache while agents with a vasodilatory action provoke or worsen headache. According to this theory, migraine is caused by an abnormal dilatation of intracranial blood vessels which leads to an excitation of sensory fibers innervating these blood vessels (Ray and Wolff, 1940). However, no empirical evidence exists in support of this theory. An alternative and more recent theory proposed that migraine is caused by a chemical activation of meningeal perivascular sensory fibers (Moskowitz *et al.*, 1983). Due to inflammation, ions, protons, and inflammatory agents that activate and sensitize peripheral nociceptors are released in the vicinity of sensory fibers that innervate the dura. There seems to be experimental evidence in favor of this latter theory.

In the first part of this paper, I will describe in more detail two animal models of migraine and facial pain that have been developed over the past decade. Thereafter, I will present some recent findings from functional neuroimaging studies that may help to come to a better understanding of the physiopathology of facial pain.

Animal models of facial pain

One of the first experimental models of facial pain in animals was developed by King and colleagues (1956). These authors injected an alumina gel suspension into the caudal portion of spinal V in cats. The majority of the animals did not show particular effects in the days following the injection. However, one to two months after injection, the animals began to lose hair from the eyebrow and the upper lip homolateral to the side of injection. They avoided cleaning this skin area. Gradually, the animals developed over-reaction to tactile stimulation on the side of the face corresponding to the side of the alumina gel injection. Finally, animals avoided all contacts with the affected side of the face, even refusing to eat. The real interest in animal models of facial pain arose however in the 90's. It formed a trigeminal spinoff of a general interest in the development of appropriate animal models of chronic pain at that time.

A number of alternative animal models of facial pain have provided us useful instruments to study the underlying physiopathology of facial pain. I will present two models that have been widely used and have been validated : chemical stimulation of the intracranial dura and infraorbital nerve ligation. There are many other animal models available (see De Vries *et al.*, 1999 for a recent review on animal models of migraine).

Chemical stimulation of the intracranial dura

Strassman and Burstein (1996) developed an animal model of migraine by chemical stimulation of the dura. In brief, rats are anesthetized and a craniotomy is performed. A recording electrode is inserted in the nucleus caudalis and the response characteristics of these neurons to mechanical (stimulation with a von Frey hair) and thermal stimulation of the dura and the orofacial skin are assessed. Thereafter, an inflammatory soup (a mixture of serotonin, histamin, bradykinin, and prostaglandin) or a low pH phosphate buffer is topically applied to the dura for 2 to 5 minutes and the response characteristics of nucleus caudalis neurons to the same mechanical and thermal stimuli are assessed again.

Responses of dura-sensitive neurons

Nucleus caudalis neurons with receptive fields on the dura showed significant changes in their spontaneous firing after chemical stimulation of the dura. In some neurons, the increase in spontaneous activity was limited to the application period ; in other neurons, increased spontaneous activity outlasted the period of chemical stimulation for more than 10 minutes. Mechanical thresholds to dural indentation were significantly reduced and neurons showed an increased responsiveness to stimulation. This sensitization occurred in all classes of neurons (low-threshold (LT), wide-dynamic range (WDR) and high-threshold (HT) neurons). The sensitization sometimes persisted up till 10 hours after chemical stimulation.

A disadvantage of the model by Strassman and Burstein is that the experiments require that the animals are anesthetized. Therefore, it cannot be verified behaviourally whether the used stimulation is painful or not. Yamamura and colleagues (1999) provided some indirect physiological evidence in support of the hypothesis that pain is produced by the stimuli used in these experiments. They argued that noxious stimulation which causes tissue damage produces pressor responses and, therefore, that increased pressor responses should occur after chemical sensitization of the dura. Before application of the chemical agents, only pinching (but not brushing or mild touch) of the dura produced increases in blood pressure in the anesthetized animals. After chemical sensitization, marked blood pressure increases were also observed in response to brush or very light touch applied to the dura. Together, these data suggest that after neuronal hypersensitization, innocuous stimuli do become painful (allodynic).

Responses of neurons with cutaneous receptive fields

Chemical stimulation of the dura also resulted in increased cutaneous mechanosensitivity. Responses to innocuous and noxious mechanical stimulation of the cutaneous receptive field were examined before and at varying times after topical application of the chemical agents to the dura Already 15 min after dural stimulation, neurons showed significant increases in their responses to brush and pressure. In some cases, a tenfold drop in response threshold was observed. Again, increased mechanical responsiveness was observed in all classes of neurons. The response threshold to heat and cold stimulation also significantly dropped after chemical stimulation. The hypersensitivity to cutaneous stimulation remained after blocking the input from the dura by local anesthetics. This suggest that central mechanisms do contribute to the observed hypersensitivity. Both the intracranial and extracranial receptive fields expanded after chemical stimulation.

Implications for the understanding of the mechanisms involved in migraine in man

The experimental findings listed above suggest that the extracranial hypersensitivity that is often observed in headache may have an intracranial origin. The chemogenic agents that were used in this model, bradykinin, histamine, serotonin, and prostaglandin, are found endogenously and are released locally during inflammatory states. They are probably released in the vicinity of the dural sinuses by increased plasma extravasation and mast cell degranulation as a result of neurogenic inflammation (Goadsby, 2000 ; Moskowitz, 1993). Some of the von Frey hairs that were used and were able to drive nucleus caudalis neurons after chemical sensitization did not produce any visible indentation of the sinus. They exerted forces around 0.08 g which are probably in the same order of magnitude as the forces exerted by heart beat pulsation. This may explain why in headache patients, pain may be provoked by physical activities that increase intracranial pressure such as coughing, bending over, climbing a staircase, etc. The above results further suggest that both peripheral and central sensitization may contribute to allodynia in headache patients. First, peripheral fibers innervating the dura lower their mechanical threshold which may explain hypersensitivity to changes in intracranial pressure. On the other hand, central sensitization of

medullary dorsal horn neurons receiving input from the dura, skin, hair follicles, and the cornea may lower their response threshold to mechanical and thermal stimulation which may be at the basis of the extracranial hypersensitivity.

Parallels between human psychophysical findings and animal data

Burstein and colleagues (2000b) recently assessed the association between migraine and cutaneous allodynia. They studied the presence of allodynia in different body regions in 33 patients suffering from migraine. They tested for the presence of tactile, heat and cold allodynia before and during a migraine attack. Five of the patients showed allodynia only in the ipsilateral face during the migraine attacks. Seven patients displayed allodynia in the ipsilateral and the contralateral face. Another 7 patients suffered allodynia in the ipsilateral and contralateral face and in one remote body area (arm). Finally, the largest group of patients (n = 14) had allodynia in the ipsilateral face and in three additional body regions. The observed allodynia in the remote body regions was sometimes quite dramatic. To give an example, in one migraine patient the threshold to painful von Frey stimulation on the arm contralateral to the migraine pain dropped from 281 g before the attack to 1.5 g. In the same patient, heat pain threshold on the same arm dropped from 47 to 36 degrees and cold pain threshold rose from 10 till 28 degrees. Taken together, these data indicate that in the vast majority of the migraine patients, cutaneous allodynia is present in body areas remote from the migraine zone. In a subsequent study, the same authors studied the time course of the spread of the allodynia in a 42-year-old migraine patient (Burstein *et al.*, 2000a). One hour after the onset of the migraine attack, mechanical and cold allodynia were present in the ipsilateral forehead. After two hours, the allodynia had spread to the contralateral head and the ipsilateral arm. Four hours after the onset of the migraine, heat allodynia became also evident and the mechanical and cold allodynia further increased in magnitude. Based on these psychophysical observations, the authors developed the following three-stage hypothesis of sensitization. In the first few minutes following the onset of migraine, sensitization of peripheral nociceptors takes place. This sensitization mediates the symptoms of intracranial hypersensitivity. This is followed by a second-order neuron sensitization, which mediates the allodynia on the ipsilateral head. The next stage is a third-order neuron sensitization which is the consequence of the barrage of impulses in the second-order neurons and which mediates the development of contralateral head and ipsilateral forearm allodynia after 2h. This is an attractive hypothesis that should be tested in a neurophysiological animal experiment. The observed time profile in spontaneous pain and allodynia showed many parallels with the time profile of the neurophysiological observations in rats (increased spontaneous activity and decreased mechanical and thermal thresholds to dural and extradural stimulation). These similarities in the characteristics of the allodynia in migraine patients and in rats after chemical stimulation of the dura leans support for the validity of the animal model as an experimental model of migraine.

Some anatomical considerations

Organs of the orofacial region (eyes, nose, mouth) are of great importance for behaviours that are essential to our fitness and survival such as ingestive, defensive, and exploratory behaviour. It is generally acknowledged that the hypothalamus plays a major role in these behaviours. Therefore, it seems likely that neurons from the orofacial region project to this brain area. This hypothesis was recently tested in a very elegant combined electrophysiological and neuroantomical study (Malick *et al.*, 2000). These authors recorded from 72 hypothalamic-projecting neurons in the caudal medulla and upper cervical spinal cord that had trigeminal receptive fields. The majority of the neurons were found in laminae I-V of the dorsal horn at level C1 or in the nucleus caudalis and were considered as trigeminohypothalamic tract (THT) neurons. Their receptive fields were restricted to the innervation territory of the trigeminal nerve (tongue, lips, dura, vibrissae, and cornea). The majority of these neurons (80%) responded to nociceptive stimulation and were classified as either nociceptive specific or wide dynamic range neurons. The neurons in the adjacent lateral reticular formation were considered reticulohypothalamic (RHT) neurons. These THT neurons had large receptive fields, including the orofacial region and large extracephalic skin areas, sometimes covering the whole body. These findings show that nociceptive signals from the facial region may reach the hypothalamus through two different pathways.

Infraorbital nerve ligation

An alternative model of facial pain was proposed by Vos and colleagues (1994). In great distinction with the model developed by Strassman and colleagues, in the model by Vos the observed changes in pain responsiveness can be assessed in the awake, behaving animal. The infraorbital nerve constriction (IoN) model can be seen as a trigeminal variant of the popular nerve constriction injury model developed by Bennett and colleagues (1992). These authors reported that after loosely ligating the rat sciatic nerve, a behavioural syndrome develops that is characterized by thermal and mechanical

allodynia and possibly also spontaneous pain. In the IoN model, the ligatures are placed around the infraorbital nerve. The first days following the IoN, animals show a decreased responsiveness to mechanical stimulation applied inside the IoN territory. Thereafter, mechanical responsiveness gradually increases. Twenty to 40 days after IoN constriction, mechanical allodynia reaches its maximal amplitude. This allodynia is not only present in the ipsilateral but also in the contralateral IoN nerve territory and outside the IoN territory. The mechanical allodynia remains present for at least 4 months. It is unclear whether cold and thermal allodynia are also present since the authors didn't test for their presence. However, they observed changes in spontaneous behaviour (decreased exploratory behaviour, increased freezing and grooming) indicative for the presence of spontaneous pain. In a subsequent study, Vos and colleagues (2000) studied the response characteristics of thalamic VPM neurons before and after IoN constriction injury. In normal rats, the vast majority (67%) of the VPM neurons responded to vibrissa, hair movement, 17% to mild pressure and another 17% to pinch or pinprick. These figures change dramatically after IoN ligation : only 12% of the neurons responded to vibrissa, hair movement, 49% responded to mild pressure and 40 % to pinch or pinprick. In addition, the number of spikes and the duration of the neuronal response to mild pressure significantly increased after IoN injury. Both phenomena were present in the ipsilateral and contralateral VPM, concordant with the behavioural observations. This abnormal response to mild pressure was abolished after the administration of lidocaine.

Neuroimaging studies of facial pain

We will make a jump now from animal models of facial pain to functional neuroimaging studies of clinical or experimentally induced facial pain. Modern neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) may be of great help to come to a better understanding of the cerebral mechanisms involved in facial pain. Compared to classical techniques such as single-unit recordings, they have the great advantage that they allow acquiring data from all parts of the brain at the same time. Moreover, since they are minimally invasive, they can be applied as well in healthy volunteers. The first neuroimaging studies of pain processing appeared in the early 90's. PET and fMRI studies in following years confirmed the early observations that pain processing involves a distributed cortical and subcortical network in the brain. Among the areas that appear to be most often activated upon the application of a painful stimulus are the insular cortex, primary and secondary somatosensory cortices, anterior cingulate cortex, thalamus, posterior parietal and prefrontal cortices, cerebellum, and supplementary motor cortex (see Peyron *et al.,* 2000 for a recent review).

Clinical forms of facial pain

The neuroimaging studies on facial pain can be grossly divided in two categories : those that focussed on the aura in migraine and those in which the main focus of the study was the pain. In the following, we will discuss only results from studies focussing on the cerebral correlates of facial pain. The reader interested in the physiopathology of the aura may find more information in some recently published reviews on this topic (Aurora and Welsch, 2000 ; Cutrer *et al.,* 2000).

One of the first PET studies focussing on pain in migraineurs is the one by Weiller and colleagues (1995). These authors studied 9 patients suffering from migraine attacks that were not preceded by aura. This study revealed that migraine headache was associated with significant regional cerebral blood flow (rCBF) increases in the anterior cingulate cortex, visual and auditory association cortices, and median brainstem structures. The activation in the median brainstem even persisted after effective treatment of the headache with sumatriptan. The authors concluded that a migraine "generator" might be present in the median brainstem. Shortly after this report, the Karolinska group published a study on cluster headache (Hsieh *et al.,* 1996). In this study, 7 right-handed patients suffering from episodic cluster headache were investigated. Cluster headache was experimentally induced by sublingual administration of 1 mg of nitroglycerin. Patients were scanned in the following experimental conditions : during rest (no pain) ; after administration of nitroglycerin but before onset of the cluster headache attack ; during headache and after relief of headache by sumatriptan. During the headache scans, average pain ratings were around 7 on a 10-cm VAS scale. In the other 3 conditions, patients were painfree. During the cluster headache attack, a significant increase in rCBF was observed in the right anterior cingulate cortex, the perigenual cingulate region, primary motor cortex, insular (bilateral), and inferior frontal cortex. Significant rCBF increases were also noticed in the cavernous sinus. The rCBF increase in the cavernous sinus already started before pain onset (after nitroglycerin intake), but continued to increase in the headache scans. No activations were found in the primary or secondary somatosensory cortices, hypothalamus or periaqueductal grey. This is in contrast with results of more recent PET studies (see further). These results suggest a preference of the right hemisphere for facial pain, especially the anterior cingulate and the medial prefrontal cortices, in attributing emotional valence and attention

to the pain suffering. A right hemispheric preponderance was also reported by Hari *et al.* (1998) in experimental facial pain. Hsieh and colleagues (1999) also studied blood flow changes in trigeminal neuropathic pain. Five right-handed patients suffering from trigeminal neuropathic pain were studied. These patients were treated with motor cortex stimulation because their trigeminal pain was refractory to conventional pain treatment. Patients were scanned during their habitual pain state and during pain relief produced by motor cortex stimulation. Average pain scores in the 2 conditions were resp. 8.8 and 1.1 on a 10-cm VAS scale. Increased rCBF was detected in the right caudal ACC and anterior limbic thalamus, while a decreased activity was observed in the right medial prefrontal cortex (BA 9/32) during the habitual-pain state, in comparison with the pain-alleviated state regardless of the pain side. Like in the cluster headache patients, no activation was found in the primary or secondary somatosensory cortices.

May, Goadsby and colleagues performed a series of neuroimaging studies in patients with cluster headache. Cluster headache is a rare but extremely painful form of headache. It is nearly always limited to one side of the face and comes in bouts of attacks which may last from days till months. Between the bouts, the patients are asymptomatic. May and colleagues (1998) studied 9 cluster headache patients while they were painfree and after the induction of cluster headache by inhalation of nitroglycerin. In contrast with the earlier findings reported by Hsieh *et al.* (1996), a prominent activation in the ipsilateral inferior hypothalamus was found. Additional rCBF increases were observed in the insula (bilaterally), right anterior cingulate cortex, right inferior frontal cortex, contralateral thalamus, and cerebellum. No activation was reported in primary or secondary somatosensory cortices nor in the brainstem. The lack of activation in the brainstem is in contrast with activation of this area during migraine attacks (Weiller *et al.*, 1995). In a following study, the authors looked at possible structural changes in the brain of cluster headache patients. Thereto they used a method called voxel-based morphometry (Ashburner *et al.*, 2000). This is an objective and automated method that is used for analyzing structural changes in the brain. It was found that in cluster headache patients, structural changes were present in the inferior posterior hypothalamus (May *et al.*, 1999). This region corresponded with the area that was found to show a significant rCBF increase in their previous study. The authors therefore concluded that a brain abnormality in the hypothalamic region may be at the basis of cluster headache.

We recently studied a patient with facial neuropathic pain who was treated with thalamic stimulation for pain control (Kupers *et al.*, 2000). The patient's pain started after surgical resection of an adenocarcinoma in the right cheek. Since this operation, the patient complained of a stinging and shooting pain in the right side of the face (V2). The patient was successfully treated with thalamic stimulation. We scanned this patient in the following 3 conditions : during facial pain (produced by switching off the thalamic stimulator for more than 12 hours), during thalamic stimulation (no pain, stimulation), and immediately after thalamic stimulation when pain had completely resided (no pain, no stimulation). We compared rCBF before and after thalamic stimulation. Facial pain was associated with rCBF increases in the contralateral insula, prefrontal cortex, perigenual cingulate, brainstem, and the hypothalamus.

Experimentally induced forms of facial pain

May and colleagues (1998) used a model of capsaicin induced experimental facial pain. Capsaicin is the pungent ingredient of red hot chili peppers. Upon application, it produces a burning pain that peaks within a few seconds after injection and then gradually declines over a period of about 15 minutes. A small amount of capsaicin was subcutaneously injected in the right forehead of 7 right-handed, headache-free healthy volunteers. Subjects were scanned before and after injection of capsaicin. All subjects reported that capsaicin produced pain and autonomic symptoms (tearing and rhinorrhea). Significant capsaicin-pain induced rCBF increases were found in the insula (bilaterally), the right anterior cingulate, cerebellum, contralateral thalamus, and cavernous sinus. No rCBF increases were observed in the hypothalamus, in contrast with the results obtained by the same authors in cluster headache. Based on this differential hypothalamic response in on the one hand cluster headache (significant rCBF increase in hypothalamus) and on the other hand migraine and experimental cranial pain (no hypothalamic rCBF increase), the authors concluded that hypothalamic activity is a typical characteristic of cluster headache. In contrast, the rCBF response in the cavernous sinus was present both in cluster headache and capsaicin induced pain and was therefore thought to be a reflex response to pain rather than the generator of pain.

Some caution is needed in associating cluster headache with hypothalamic activation. First, the earlier described electrophysiological results obtained in rats have shown the existence of hypothalamic projecting neurons in the caudal medulla and upper cervical cord. These neurons were activated by applying noxious stimuli such as pinch, squeeze and noxious heat to the trigeminal nerve territory under normal physiological circumstances. This suggests that many different types of painful stimuli applied in the trigeminal area should be able to drive hypothalamic neurons.

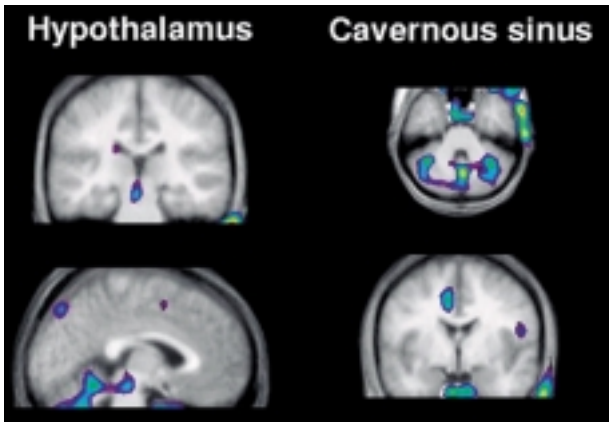

FIG. 1.

Second, other PET studies have shown that traumatic nociceptive stimuli applied outside the facial region can also induce rCBF increases in the hypothalamus. For instance, a significant rCBF increase in the hypothalamus has also been reported in response to the intracutaneous injection of ethanol in the upper arm (Hsieh *et al.*, 1996). Kupers *et al.* (2000) recently performed a PET study on experimentally induced myofascial pain. Ten headache-free healthy volunteers participated in this study. Experimental pain was induced by the intramuscular injection of hypertonic saline into the masseter muscle. This produces an intense and very unpleasant pain sensation. Subjects were scanned before and during experimentally induced myofascial pain. Besides activations in a number of areas that were also activated in the capsaicin study (insula, anterior cingulate, cavernous sinus), hypertonic saline produced a significant rCBF increase in the hypothalamus (Fig. 1).

Taken together, the results of PET studies on experimental and clinical forms of facial pain do suggest that intracranial dilation of blood vessels is not specific to any particular type of clinical headache. Intracranial vessel increase, in particular of the cavernous sinus, is probably the result of a trigeminoparasympathetic reflex, driven by pain. The particular role of the hypothalamus in the genesis of specific forms of facial pain is still not fully established. Whereas studies in patients with cluster headache seem to argue for a pivotal role of this area in the genesis of this syndrome, other PET studies have questioned the specificity of the hypothalamic activation for cluster headache since a hypothalamic activation has also been described in others forms of facial pain. A common denominator of the hypothalamic activations is that they seem to occur in conditions which provoke fear and form a threat to the integrity of the body such as in conditions of extreme pain. This more general role of the hypothalamus also seems easier to reconcile with electrophysiological observations in animals. Another intriguing aspect of the PET results is that they all failed to show activation in the primary and secondary somatosensory cortices. Instead, strong activations in the anterior cingulate, anterior insula, and prefrontal cortex were reported. These may underlay the high unpleasantness of facial types of pain.

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