Early reports

Hypothalamic activation in cluster headache attacks

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Summary

Background Cluster headache, one of the most severe pain syndromes in human beings, is usually described as a vascular headache. However, the striking circadian rhythmicity of this strictly half-sided pain syndrome cannot be readily explained by the vascular hypothesis. We aimed to assess changes in regional cerebral blood flow (rCBF) in patients with cluster headache.

Methods We used positron emission tomography (PET) to assess the changes in rCBF, as an index of synaptic activity, during nitroglycerin-induced cluster headache attacks in nine patients who had chronic cluster headache. Eight patients who had cluster headache but were not in the bout acted as a control group.

Findings In the acute pain state, activation was seen in the ipsilateral inferior hypothalamic grey matter, the contralateral ventroposterior thalamus, the anterior cingulate cortex, and bilaterally in the insulae. Activation in the hypothalamus was seen solely in the pain state and was not seen in patients who have cluster headache but were out of the bout.

Interpretation Our findings establish central nervous system dysfunction in the region of the hypothalamus as the primum movens in the pathophysiology of cluster headache. We suggest that a radical reappraisal of this type of headache is needed and that it should in general terms, be regarded as a neurovascular headache, to give equal weight to the pathological and physiological mechanisms that are at work.

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Introduction

The pain of cluster headache is perhaps the most severe known to human beings. Women who have such headaches describe each attack as being worse than childbirth. The syndrome is clinically well defined[1] and despite its recognition in published work for more than two centuries[2] its pathophysiology is poorly understood.

The excruciatingly severe one-sided pain is likely to be mediated by activation of the first (ophthalmic) division of the trigeminal nerve, whereas the autonomic symptoms are a result of activation of the cranial parasympathetic outflow from the VIIth cranial nerve.[3] The relapsing-remitting course,[4] its seasonal variation,[4] and the clockwise regularity[5] are characteristic but unexplained features of the disorder.

The striking circadian rhythmicity of cluster headache has led to the suggestion of a central origin for its initiation.[6,7] Substantially lowered concentrations of plasma testosterone during the cluster headache period in men provided the first evidence of hypothalamic involvement in cluster headache.[8] This finding was further supported by a reduced response to thyrotropin-releasing hormone[9] and a range of other circadian irregularities that have been reported in patients who have cluster headaches.[10] Melatonin is a marker of the circadian system and a blunted nocturnal peak melatonin concentration and complete loss of circadian rhythm have been reported in patients who have cluster headache.[10] The endogenous circadian rhythm is run by an oscillator in the suprachiasmatic nuclei in the ventral hypothalamus and reacts to temporal environmental cues of light conditions via a retino-hypothalamic pathway. The hypothalamus, or a closely related structure, is a candidate site for triggering the acute attack of cluster headache.

Positron emission tomography (PET) is probably the best technique for visualising in-vivo changes in regional cerebral blood flow (rCBF) in human beings. Modern high-resolution PET allows the detection of subtle changes in rCBF during defined behavioural tasks and provides an index of synaptic activity relating networks of regions to tested brain functions.[11]

Cluster headache attacks can be elicited with nitroglycerin during the active period without significant side effects.[5] Nitroglycerin-provoked and spontaneous cluster attacks are comparable[3,12] and nitroglycerin does not substantially alter rCBF.[13] The headache can be rapidly and effectively aborted with sumatriptan. This approach was therefore used to detect brain regions with increased blood flow during nitroglycerin-induced cluster attacks, focusing our interest on the hypothalamic region.

Methods and patients

Nine right-handed men (age 25–62 years, mean 43 years) with active chronic cluster headache, according to the Headache Classification Committee of the International Headache Society,[1]

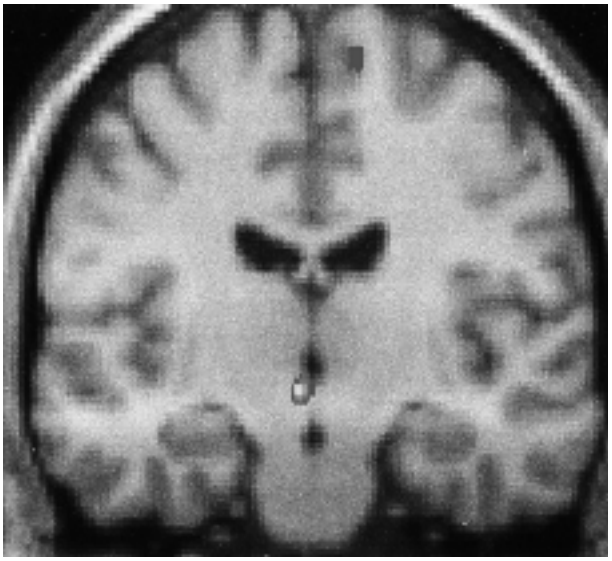

Figure 1: **Comparison of nitroglycerin-induced acute cluster-headache attack and rest (no pain) in nine patients with active chronic cluster headache**
Activations during the attack are shown as statistical parametric maps that show the areas of signfiicant rCBF increases (p<0·001) in colour superimposed on an anatomical reference derived from a T1-weighted MRI. The left side of the picture is the left side of the brain.

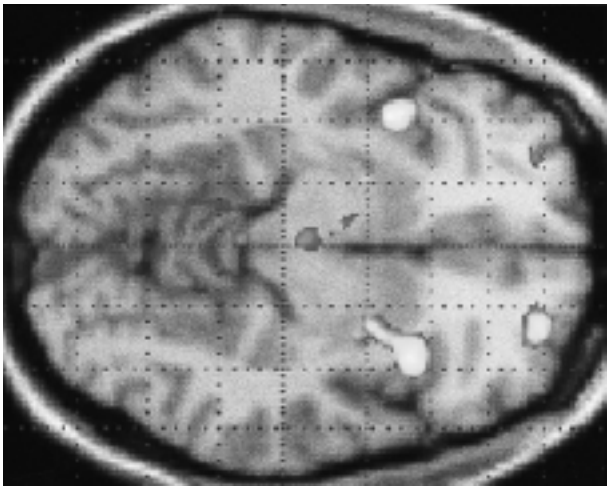

Figure 2: **Comparison of nitroglycerin-induced acute cluster headache attack and rest (no pain) condition in nine patients with active chronic cluster headache**
The activations during the attack are shown as statistical parametric maps which show the areas of significant rCBF increases (p<0·001) in colour superimposed on an anatomical reference derived from a T1-weighted MRI. The anterior part of the brain corresponds to the right side of the picture, the posterior parts to the left side, the left side of the brain corresponds to the top of the image, and the right side to the bottom.

were studied during an induced acute headache attack (study group). Acute cluster headache was provoked by inhalation of nitroglycerin (1·0–1·2 mg).[5] All patients studied were not treated prophylactically for cluster headache and were otherwise healthy. Eight patients with a history of cluster headache but who were not having a headache bout (age 36–61 years, mean age 49 years) had a PET scan by the same study design (control group). None of the control patients had a cluster headache attack after nitroglycerin was applied. Informed consent was obtained from all patients and the study was approved by the Ethics Committee of the National Hospital for Neurology and Neurosurgery, London.

Design

During the active headache period each of the nine study patients had 12 or 13 consecutive scans at four times: baseline; after application of nitroglycerin; after onset of headache; and when headache-free, after treatment with subcutaneous sumatriptan (6 mg). Each of the eight controls had 12 consecutive scans by the same design. Since none of the patients in this group had a cluster headache attack after taking the nitroglycerin, we defined scans for the second and third condition according to the mean number of scans for these conditions in the study group. For each scan, patients rated their headache intensity with a visual analogue scale (0=no pain, 10=the most severe pain). Participants had their eyes closed during all scans.

Data acquisition and analysis

PET scans were done with an ECAT EXACT HR+ scanning system (CTI Siemens, Knoxsville, TN, USA) in three-dimensional mode with septa retraced. An antecubital vein cannula was used to administer the tracer, about 350 mBq of $H_2{}^{15}O$. The activity was flushed into patients over 20 s at a rate of 10 mL/min. The data were acquired in one 90 s frame beginning 5 s before the peak of the head curve. The interval between scans was 8–15 min. Attenuation correction was done with a transmission scan done at the beginning of each study. Images were reconstructed by filtered-back projection into 63 images planes (separation 2·4 mm) and into a 128 by 128 pixel image matrix (pixel size 2·1×2·1 mm^2). Statistical Parametric Mapping 97 (SPM'97; http://www.fil.ion.ucl.ac.uk/spm) was used for data analysis. Images were realigned with the first image as the reference and then coregistered with the patient's structural magnetic resonance imaging (MRI) image and finally spatially normalised into the space defined by the atlas of Talairach and Tournoux.[14] The normalised images were smoothed with a Gaussian filter of 10 mm full width at half maximum. Statistical parametric maps were derived with pre-specified contrasts,[15] to compare rCBF during headache versus rCBF during the non-headache phase after nitroglycerin application. We also addressed the question of significant rCBF differences in the study group relative to the control group with a group-by-condition interaction analysis.

Because headache is a strictly lateralised syndrome[1] we mirrored PET and MRI scans in patients with right-sided

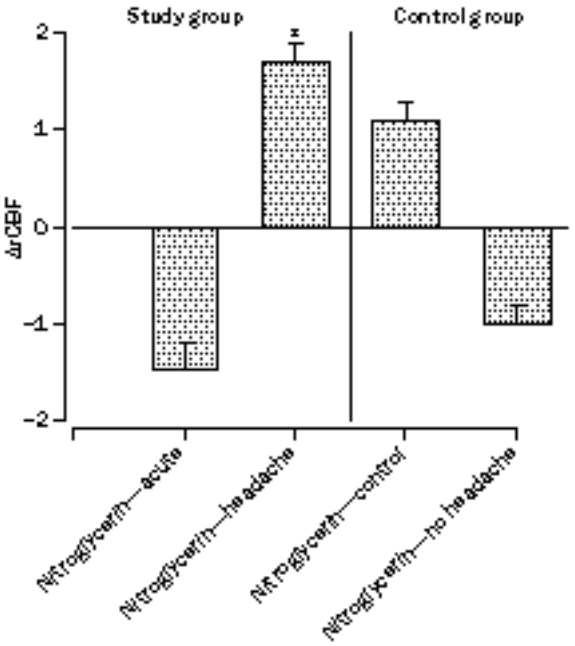

Figure 3: **Condition by group interaction**
*p<0·001 for rCBF increase in the hypothalamic area comparing headache and headache-free conditions.
ΔrCBF values are based on average grand mean set to 50 mL 100 g^{-1} min^{-1}.

Activated brain region*	Brodman area	Talairach co-ordinates (mm)			*Z* score of peak activation
		x	y	z	
Left hypothalamus		−2	−18	−8	3·68
Right thalamus		6	−12	6	5·01
Right cingulate cortex	24	2	22	24	4·9
Right frontal lobe	10	26	54	−6	4·06
Left primary motor area (face)	6/44	−40	−2	32	3·29
Right insula	13	32	10	2	4·28
Left insula	13	−40	12	−8	4·37
Left basal ganglia		−20	−12	2	4·22
Cerebellum (vermis)		−2	−38	−10	3·09

Each location is the peak within a cluster (defined as the voxel with the highest *Z*-score). *p<0·001 for all regions.

Increases in blood flow during an induced attack of acute cluster headache compared with the pain-free state

headache in the sagittal plane to be able to analyse all patients in the same analysis. The uncorrected threshold of p<0·001 was chosen because of a strong regional a-priori hypothesis based on the clinical and experimental data cited in the text.

Results

Of the nine patients in the bout, five experienced a cluster headache attack on the left side and four patients on the right side after nitroglycerin spray. Typical concurrent autonomic symptoms such as ipsilateral miosis, lacrimation, and rhinorrhoea confirmed the presence of a classic cluster headache attack. All patients described the provoked attack as being similar to spontaneous attacks. In the nine patients who had attacks of acute cluster headache, significant activations in the acute attack compared with the headache-free state were found in the ipsilateral hypothalamic grey area, bilaterally in the anterior cingulate cortex, in the contralateral posterior thalamus, the ipsilateral basal ganglia, bilaterally in the insulae (figures 1 and 2), and in the cerebellar hemispheres (table). Figure 1 shows that significant activation was detected next to the third ventricle slightly lateralised to the left and rostral to the aqueduct. The activation is ipsilateral to the pain side, lies in the diencephalon, and coincides, in the Talairach atlas,[14] with the hypothalamic grey matter. Figure 2 shows that significant activation was detected in the right frontal lobe (Brodman's area 10), bilaterally in the insula, in the cerebellum/vermis and in the hypothalamic grey matter. The activation in the hypothalamic grey area was seen only in the patients with a cluster headache attack but not in the control patients (p<0·001).

We further confirmed this result with a group (study group *vs* control group) by condition (headache-no headache) interaction (p<0·001). The difference in rCBF for the hypothalamic grey area comparing headache and headache-free conditions was significantly greater for the study than for the control group (figure 3).

Discussion

We observed areas of activation in acute cluster headache that fall into two broad groups: areas known to be involved in pain processing or response to pain, such as cingulate and insula cortex and thalamus; and areas activated specifically in cluster headache but not in other causes of head pain, notably the hypothalamic grey areas. These data suggest that primary headache syndromes share some processing pathways but equally can be distinguished on a functional neuroanatomical basis by areas of activation specific to the clinical presentation.

Studies with PET have repeatedly given results that show activation of the anterior cingulate cortex on the sensation of somatic or visceral pain that are attributed to the emotional response to pain.[13,16,17] Activations in the insula have been shown after application of heat,[16,18] subacutaneous injections of ethanol,[19] somatosensory stimulation,[20] and during cluster headache.[13] Given its anatomical connections, the insula has been suggested as a relay of sensory information into the limbic system and is known to play an important part in the regulation of autonomic responses.[21] Painful stimuli are significantly effective in activating the anterior insula, a region closely associated with both somatosensory and limbic systems. Such connections may provide one route through which nociceptive input is integrated with memory to allow full appreciation of the meaning and dangers of painful stimuli. In the acute pain state the thalamus is a site where activations would most be expected. Activation of the contralateral thalamus as a result of pain is known from studies on animals[22] and functional imaging studies in human beings.[16,17] The acute pain in cluster headache, induced activation bilaterally in the cerebellar hemispheres and in the vermis. There seems to be no direct nociceptive input to the cerebellum,[23] and there is no clinical evidence that cerebellar lesions or stimulation affect pain sensation in human beings.[16] However, there are some PET studies that report an activation in this area during experimental pain.[16,24]

In contrast to migraine,[25] no brain stem activation was found during the acute attack compared with the resting state. This finding is remarkable because migraine and cluster headache are often discussed as associated disorders and similar compounds, such as ergotamine and sumatriptan, are used in the acute treatment of both types of headache. These data suggest that while primary headaches, such as migraine and cluster headache, may share a common pain pathway (the trigeminovascular innervation), the underlying pathogenesis differs substantially as might be inferred from the different patterns of presentation and responses to preventive agents.[26]

Substantial activations ascribable to cluster headache were observed in the ipsilateral hypothalamic grey area when compared with the headache-free state. Just as it is striking that no brain-stem activation occurs, which is in contrast to acute migraine,[25] we have seen no hypothalamic activation in experimental pain induced by capsaicin injection into the forehead.[27] Injection into the forehead would activate first division (ophthalmic) afferents which traverse the trigeminal division responsible for pain activation in cluster headache. Thus two other types of first division trigeminal nerve pain, while sharing neuroanatomical pathways with cluster headache, do not give rise to hypothalamic activation. Moreover, in the eight control patients who did not experience a headache after taking nitroglycerin, rCBF in the region of the hypothalamic grey area was not increased. This finding implies that the activation we have observed is involved in the pain process in a permissive or triggering manner rather than simply as a response to first division nociception per se. Hypothalamic activation in traumatic nociception has been observed in the hypothalamus proper and is a different more rostral area than we report.[19] Moreover, Hsieh and colleagues[19] report changes contralateral to the pain, whereas we report changes that are ipsilateral and in the hypothalamic grey

area in the region of the circadian pacemaker neurons which is, therefore, an anatomically distinct area on the opposite side of the brain. Given that this area is involved in circadian rhythm and sleep-wake cycling, our data establish an involvement of this area of the hypothalamus as a primum movens in the acute cluster attack.

Cluster headache has been attributed to an inflammatory process in the cavernous sinus and tributary veins.[28] Inflammation has been thought to obliterate venous outflow from the cavernous sinus on one side, thus injuring the traversing sympathetic fibres of the intracranial internal carotid artery and its branches. According to this theory, the active period ends when the inflammation is suppressed and the sympathetic fibres partially or fully recover. This theory is based on abnormal findings with orbital phlebography in patients with cluster headache,[29] and the fact that nitroglycerin and other vasodilators can induce a cluster attack.[5] However, given the circadian rhythmicity and unilaterality of the symptoms, a purely vasogenic cause cannot explain the entire picture of cluster headache.[30] Moreover, the frequency and pattern of pathological findings at orbital phlebography in cervicogenic headache, migraine, and tension-type headache is similar to that in cluster headache.[31] Given that we have found an increased signal in the region of the cavernous sinus in the patients with acute cluster headache in this study and after capsaicin injection to the forehead in another PET study,[27] it seems likely that the vascular changes are an epiphenomenon of activation of the trigeminovascular system.[32]

A radical reappraisal of the pathophysiology of cluster headache is needed. Our data establish that cluster headache, far from being a primarily vascular disorder, is a condition the genesis of which is to be found in the central nervous system in pacemaker or circadian regions of the hypothalamic grey matter. Further, we suggest that both cluster headache and migraine might usefully be regarded are neurovascular headaches to include the neural contribution to these important clinical syndromes.

Contributors

All five investigators contributed to the design of the study and to the writing of the paper. Arne May was involved in planning, study coordination, and analysis. Anish Bahra was involved in recruiting the patients and scanning. Christian Büchel was involved in the statistical analysis. Richard Frackowiak and Peter Goadsby were involved in planning, study coordination, and review of the data.

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