

# Brain stem activation in spontaneous human migraine attacks

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**Evidence from animal experiments shows that the brain stem is involved in the pathophysiology of migraine. To investigate human migraine, we used positron emission tomography to examine the changes in regional cerebral blood flow as an index of neuronal activity in the human brain during spontaneous migraine attacks. During the attacks, increased blood flow was found in the cerebral hemispheres in cingulate, auditory and visual association cortices and in the brain stem. However, only the brain stem activation persisted after the injection of sumatriptan had induced complete relief from headache and phono- and photophobia. These findings support the idea that the pathogenesis of migraine is related to an imbalance in activity between brain stem nuclei regulating antinociception and vascular control.**

Vascular changes are no longer seen as the primary cause for head pain in migraine. Recent experimental and clinical data suggest a temporary aseptic perivascular inflammation in the dura from trigeminal antidromic release of neuropeptides such as calcitonin gene-related peptide (CGRP), substance P and other tachykinins<sup>1</sup>. Proponents of other theories discuss a primary imbalance of the trigeminal nociceptive, the midbrain endogenous antinociceptive system (periaqueductal grey (PAG) and dorsal raphe nucleus (DRN)) and the autonomic control of cerebral and dural blood flow (DRN and locus coeruleus)<sup>2,3</sup>. The importance of the brain stem for the genesis of migraine is further underlined by the presence of binding sites for specific antimigraine compounds on these structures (ref. 4 and C. Waeber, pers. commun.). The only direct clinical evidence for the brain stem as prime mover in migraine was reported by Raskin in non-headache patients who developed migraine-like episodes after stereotactic intervention by creating a lesion of the PAG and more specifically the DRN (ref. 5). Interestingly, these headaches responded to specific serotonergic agonists.

In previous studies of cerebral blood flow (rCBF) in migraine, investigators tried to establish gross changes in cortical perfusion of the cerebral hemispheres as an explanation for either the aura or the headache (for an overview, see refs 6, 7). The results have been quite heterogeneous, mainly because of methodological differences. Patients with or without aura were intermixed and some were studied late, some early in the attack. Varying techniques with their inherent limitations were used. Perhaps most consistently a focal hypoperfusion in the posterior regions of the brain has been found during the aura of induced attacks using the Xenon-inhalation technique<sup>6,8</sup>.

During the headache phase of migraine in cases without aura, no rCBF changes have been reported in most instances, using single photon emission computed tomography (SPECT) techniques<sup>9,10</sup>. Except for one study, published as an abstract on oxygen metabolism<sup>11</sup>, there is just one case report using positron

emission tomography (PET) to measure rCBF, of a woman who by chance happened to experience a migraine attack (without aura) while lying in the scanner undertaking a visual stimulation task. She showed a hypoperfusion starting at the posterior part of the brain and spreading gradually forward during the first 80 minutes of the attack<sup>12</sup>. The difference with regard to the SPECT studies may be attributed to the very early measurements. None of these rCBF studies examined the brain stem, which, as outlined above, plays an important role in the pathophysiology of migraine.

Positron emission tomography (PET) may represent the best currently available technique for assessing *in vivo* changes in rCBF in humans. Modern high-resolution PET scanning allows the detection of subtle changes in rCBF during defined behavioural tasks and provides an index of synaptic activity relating networks of regions to the tested brain function<sup>13,14</sup>. We used this approach to detect brain regions with increased blood flow during spontaneous and unmedicated migraine attacks, focusing on the brain stem. As the symptoms of the aura vary and attacks with or without aura are mixed in the same individual, we chose to study cases without aura. We felt this would eliminate confounding factors and would enable us to more easily detect a common basic mechanism underlying the headache in migraine.

## Brain regions active during migraine attacks

In nine patients with right-sided headache, studied within six hours after the onset of migraine symptoms, significantly higher rCBF values compared with the headache-free interval were found in the cerebrum bilaterally in the cingulate cortex (Brodmann area (BA) 24/32), inferior anterocaudal cingulate cortex (BA 25; on the left side only), auditory association cortices (BA 21 and 22) and at the parieto-occipital junction in the visual association cortex (BA 19/39). There was a strong rCBF increase during the attack (+11%) in brain stem structures over several planes (from -23 mm to -11 mm with respect to the intercommissural

line). This activation was slightly lateralized to the left, anterior to the aqueduct and posterior to the corticospinal tract and the cranial nerve nuclei with the focus of maximum significance located at +4, -26, -16 mm in Talairach coordinates (Fig. 1).

### Effect of sumatriptan

Injection of 6 mg sumatriptan (a 5-HT<sub>1D</sub>-agonist) subcutaneously relieved the patients from their headaches and other concomitant symptoms, such as nausea or phono- and photophobia. PET scanning at this stage (usually about 30 minutes after the first scan) showed no increase in blood flow in the cortical areas of the hemispheres compared with the headache-free interval. However, the activation in the brain stem persisted (Table 1).

### Discussion

#### Brain stem activation during migraine

This is the first report of a strong brain stem activation in association with an acute, spontaneous migraine attack in patients with migraine without aura. Activation was slightly lateralized, contralateral to the side of the headache. It seems reasonable to attribute this activity to brain stem grey matter, as changes in rCBF appear to be more related to changes in synaptic activity of the neurons than to changes in white matter<sup>14</sup>. It is beyond the resolution of the PET camera to attribute foci of rCBF increases to distinct brain stem nuclei. However, the foci of maximum increase coincided, in the Talairach space, with the anatomical location of the DRN and the locus coeruleus. Dysfunction in the regulation of these brain stem nuclei, which are involved in antinociception and extra- and intracerebral vascular control, provides a far-reaching explanation for many of the facets of migraine<sup>2,5</sup>. It is tempting to consider the observed activation in the brain stem as the first direct visualization of the postulated migraine centre in humans.

#### Activation of cortical brain regions

Activation of the cingulate cortex (dorsal cingulate, BA 23 as well as infero antero-caudal cingulate, BA 25) has repeatedly been reported in PET studies on sensation of somatic or visceral pain and has been attributed to the emotional response to pain<sup>15,16,17</sup>.

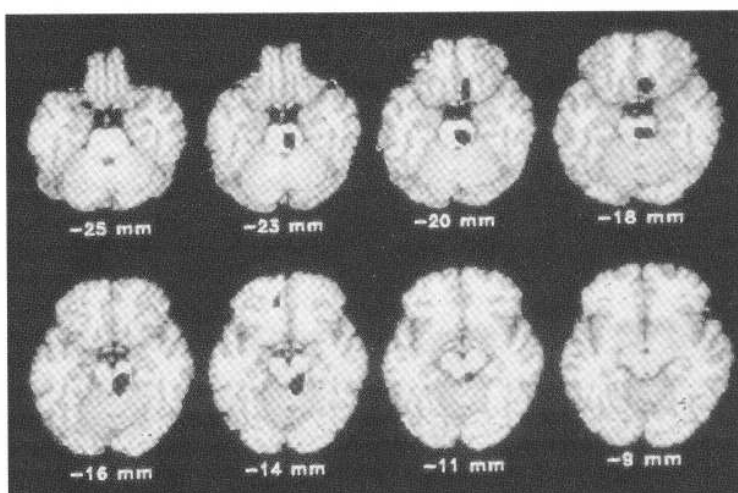
**Table 1** Cerebral blood flow during migraine attack after treatment and during headache-free intervals

Brain regions (x, y, z coordinates)	rCBF (ml min <sup>-1</sup> 100 ml)		
	scan 1	scan 2	scan 3
<b>Bilateral areas</b>			
Left parieto-occipital junction (BA 39/ 19) (42, -58, 20)	58.4	53.3	52.7
Right parieto-occipital junction (BA 39/ 19) (-38, -56, 24)	55.1	50.3	49.7
Left temporal cortex (BA 21/ 22) (48, -34, 0)	62.8	58.1	57.1
Right temporal cortex (BA 21/ 22) (-42, -22, 4)	71.8	67.0	67.3
<b>Midline structures</b>			
Cingulate gyrus (BA 24/ 32) (-2, 18, 32)	64.4	61.4	59.1
Inferior cingulate gyrus (BA 25) (8, 12, -18)	59.9	55.2	55.5
Brain stem (4, -26, -16)	59.4	58.9	52.2

Analysis of rCBF as normalized flow during the acute attack (scan 1), after relief from headache by sumatriptan, about 30 minutes later (scan 2) and during the headache-free interval (scan 3) in areas with significantly increased blood flow during the acute attack compared with the free interval. The contrasts are tabulated in terms of the activated brain region and their Brodmann's areas, the x, y, z coordinates, according to the atlas of Talairach and Tournoux<sup>25</sup>, of each peak (defined as the pixel with the highest z-score within each activated region) and of normalized rCBF values (in ml min<sup>-1</sup> per 100 ml tissue) for each of the three conditions.

Increased blood flow during the acute attack in auditory and visual association cortices can tentatively be attributed to phono- and photophobia typically encountered in these patients. As special emphasis was put on the study of the brain stem; other areas at the top of the brain escaped scanning because of the restricted field of view of our camera.

Fig. 1 Comparison of acute migraine attack and headache-free interval in nine patients with migraine without aura. The activations during the attack are shown as statistical parametric maps that show the areas of significant rCBF increases ( $P < 0.001$ ) in red superimposed on an anatomical reference image derived from a T1-weighted MR image. Numbers refer to the relative distance to the ACPC-line (joining the anterior and posterior commissures), which is situated at 0 mm. The anterior part of the brain corresponds to the top of the image, the posterior parts to the bottom. The left side of each image is the right side of the brain. Significant increases in regional cerebral blood flow were detected over several planes in the brain stem slightly lateralized to the left, anterior to the aqueduct and posterior to the cranial nerve nuclei in the periaqueductal grey matter and midbrain reticular formation, as well as in the infero antero-caudal part of the cingulate gyrus (Brodmann area 25).



### Effect of sumatriptan

Activation of brain stem structures in acute experimental pain has been documented with PET (ref. 16). However, the brain stem activation during spontaneous migraine attacks that we report here persisted after sumatriptan had induced relief from headache, photophobia, phonophobia and other, related autonomic symptoms. Therefore, it is unlikely that this activation is only due to increased activity of the endogenous antinociceptive system<sup>18,19</sup>. It seems not to be a consequence of headache or related to the relief from headache but may be inherent to the migraine attack itself.

These findings are in line with the known presynaptic site of action for sumatriptan through 5-HT<sub>1D</sub> autoreceptors on peripheral nociceptive trigeminal fibers<sup>1</sup>. Central antinociceptive effects of sumatriptan on the trigeminal system are only described after disruption of the blood-brain barrier<sup>20</sup>. This may explain why sumatriptan and other compounds that are unable to cross the blood-brain barrier<sup>20</sup> are effective in mitigating the symptoms of migraine but are sometimes unable to terminate the actual attack. The duration of the migraine may be determined by other factors, possibly mirrored in the continuing activity of the brain stem area reported here. The headache may recur after the effect of sumatriptan with its short half-life<sup>21</sup> has worn off.

### Methods

**Patients.** Nine patients (7 female, 2 male) (29–57 years old) who had had migraine without aura for 4 to 30 years were studied during a spontaneous, acute attack of migraine with right-sided headache. Headache was classified as migraine without aura according to the Headache Classification Committee of the International Headache Society<sup>22</sup>. Three of the patients were on prophylactic treatment with 200 mg metoprolol. We do not believe this influenced the results as the patients acted as their own controls with and without a migraine attack. The study was approved by the ethics committee of the Medical School of the University of Essen. All participants signed an informed consent form.

**Design.** All nine patients were studied within 6 hours after the onset of migraine symptoms. Each patient had three rCBF measurements; (1) during the acute attack, (2) after relief from the headache (and other related symptoms) by 6 mg sumatriptan s.c. (usually about 30 minutes after the first scan) and (3) again during the headache-free interval (3 days to 4 months later). The eyes were closed during all scans.

**Data acquisition and analysis.** rCBF was measured using a <sup>15</sup>C-labelled O<sub>2</sub> integral inhalation technique (500 ml min<sup>-1</sup> at 6 MBq ml<sup>-1</sup>)<sup>23</sup> with an ECAT 953-15 PET scanner (CTI Inc., Knoxville, Tennessee). After attenuation correction (measured by a transmission scan), the data were reconstructed as 15 transaxial planes by filtered back projection with a Hanning filter with cut-off frequency of 2.5 cycles per cm. The integrated counts accumulated were used as an index of rCBF (ref. 13). The scans were realigned to each other<sup>24</sup>, filtered (low-pass Gaussian filter; 10 mm at FWHM) and transformed into a standard stereotactic anatomical space<sup>25,26</sup>. By using appropriate statistical contrasts, the main effect of migraine attack was estimated on a pixel-by-pixel basis using statistical parametric mapping (SPM; MRC Cyclotron Unit, Hammersmith Hospital, London). Covariance analysis of global differences was carried out, and comparison of the means was made by using the *t* statistic<sup>27,28</sup>.

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