Opioidergic changes in the pineal gland and hypothalamus in cluster headache: A ligand PET study

Abstract—Using PET with the opioidergic ligand [^{11}C]diprenorphine, the authors demonstrate decreased tracer binding in the pineal gland of cluster headache patients vs healthy volunteers. Opioid receptor availability in the hypothalamus and cingulate cortex depended on the duration of the headache disorder. Therefore, the pathophysiology of cluster headache may relate to opioidergic dysfunction in circuitries generating the biologic clock.

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Cluster headache (CH), a lateralized headache disorder comprising periorbital pain and ipsilateral autonomic symptoms, is characterized by circadian and seasonal periodicity. The hypothalamus has been implicated in the pathogenesis of CH because this region displayed increased brain activity during attacks¹ and structural changes have been evidenced in the same area by voxel-based morphometry.² Neuroendocrinologic alterations point to participation of biologic clock generators in the pathophysiology. The secretion of melatonin, which is mainly produced by the pineal gland and which plays a major role in the synchronization of the sleep/wake cycle, has been shown to be altered in CH,³ and oral administration has been suggested for the treatment of CH. Regarding the opioidergic system, the circadian rhythm of beta-endorphin serum levels is lacking in patients with CH,⁴ and opioids can alter the secretion of melatonin by the mammalian pineal gland.⁵ We investigated CH patients by opioidergic ligand PET.

Methods. Seven men with left-sided CH according to International Headache Society guidelines (six episodic and one chronic CH; mean age 46.9 years) and eight healthy men (mean age 45.3 years; group difference in age not significant in two-tailed *t* test; *p* = 0.85) were investigated with [^{11}C]diprenorphine (DPN) PET. [^{11}C]DPN is a competitive nonselective opioid antagonist. All patients were in bout (i.e., in an active cluster period) but out of an acute attack at the time of the scanning. Disease duration varied from 1 to 19 years (mean 7.3 years; median 7 years). Clinical MRI was unremarkable in all patients. A pain-free period of 6 hours was mandatory, and all patients were in bout for at least 2 weeks at the time of scanning. The headache frequency was between one and three attacks per day in all patients, and patients were al-

lowed to continue their prophylactic medication. Five patients were taking verapamil (with one of them additionally taking methysergide), one was taking a combination of ergotamine and valproate, and one was not taking any drugs. All participants gave written consent, and the study was approved by the local ethics committee and the radiation authorities.

PET scans were acquired with a CTI ECAT EXACT scanner (Knoxville, TN) with a total axial field of 16.2 cm. The tracer was injected as an IV bolus (mean dose 19.2 mCi in the CH group, 17.6 in the control group; two-tailed *t* test, *p* = 0.33). During the 90-minute scanning period, arterial blood was sampled for calculation of the input function and metabolite correction. The arterial input function was calculated from approximately 60 arterial samples and corrected for protein binding and for metabolites derived from a fitted curve of seven time-point values. Attenuation was corrected using transmission scanning before the [^{11}C]DPN studies, and the data were reconstructed using filtered back-projection. After realignment, voxelwise spectral analysis⁶ was applied to the dynamic image series to analyze the opioid receptor availability using the integral of the impulse response function at 60 minutes (IRF₆₀). IRF₆₀ values were chosen for the analysis as an estimate for the regional volume of distribution.

These parametric images were transformed into Talairach space using the analysis package NEUROSTAT (Ann Arbor, MI). Images were smoothed with a gaussian kernel of 10 mm full width at half maximum. A voxelwise statistical comparison of the patient and control groups was conducted with SPM2 (London, UK; unpaired *t* test). Voxels were considered to be significant if they reached a statistical threshold of *p* < 0.05 after correction for multiple comparisons on cluster or whole-brain level. Because we expected changes in the pineal gland and hypothalamus, small volume correction (SVC; *p* < 0.05) was applied on these structures (spherical volumes of interest centered around the peak coordinate, radius 10 mm, volume 4189 mm³). We performed an additional statistical parametric mapping analysis (unpaired *t* test) of the episodic patients vs controls with identical thresholds as described for the whole patient population.

Voxelwise negative covariation analysis of opioidergic binding and duration of the headache disorder in the patients with CH was performed with SPM2 (with identical statistical thresholds as noted above).

Results. The statistical analysis evidenced a decrease in DPN binding in the pineal gland (millimetric coordinate of statistical peak in Talairach space: $-4.5/-29/4.5$; *z* = 3.5; number of voxels: 15; *p* < 0.001 uncorrected and *p* < 0.05 with SVC; figures 1 and 2). In other brain structures, no decreases in opioidergic receptor availability were observed (*p* < 0.001 uncorrected), and no increase in receptor availability was noted (*p* < 0.001 uncorrected).

Subgroup analysis of only the episodic patients vs controls confirmed the results of decreased opioidergic receptor binding in the pineal gland (14 voxels; *p* < 0.001 uncorrected and *p* < 0.05 with SVC). The millimetric peak coordinate was found at $-5/-29/5$, with a *z*-score of 3.36.

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Figure 1. (A) Statistical comparison of [^{11}C]-diprenorphine PET impulse response function at 60 minutes (IRF_{60}) in the pineal gland in patients with cluster headache and healthy volunteers. Decreases in opioidergic receptor availability are superimposed in color on an anatomic reference MRI (single-subject T1 image provided by SPM) in sagittal plane ($p < 0.001$ uncorrected). (B) Statistical parametric map of the negative covariation analysis between duration of the cluster headache disorder and opioidergic receptor binding (overlaid on the single-subject T1 image provided by SPM; $p < 0.005$ for descriptive purposes). Millimetric peak coordinates for the shown foci are $-13.5/27/-11$, $4.5/31.5/-7$, and $-7/2/-13.5$. The numbers adjacent to the color stripe indicate the z-score. The transversal slice plane is located 11 mm below the commissural plane.

We observed inverse linear dependence of disease duration and opioidergic binding in the hypothalamus (ipsilaterally to the pain, 37 voxels; $p < 0.001$ uncorrected and $p < 0.05$ with SVC; peak coordinates at $-13.5/0/-11$ [$z = 3.77$] and $-7/2/-13.5$ [$z = 3.60$]) and bilaterally in the rostral anterior cingulate cortex (ACC; 14 voxels; $p < 0.001$ uncorrected, $p < 0.05$ corrected for multiple comparisons on cluster level; peak coordinates: $-13.5/27/-11$ [$z = 4.36$] and $4.5/31.5/-7$ [$z = 3.23$]; see figure 1).

Discussion. We show reduced opioid receptor binding in the pineal gland but no other brain struc-

Figure 2. Scatter plot of the [^{11}C]-diprenorphine PET binding (SPM-scaled impulse response function at 60 minutes [IRF_{60}] values) at the millimetric coordinate $-4.5/-29/4.5$ (Talairach space). The bold horizontal bars indicate the mean value for each group. The thin horizontal bars indicate the SD.

ture in patients with CH who are in bout but out of an acute attack. The trigeminal system is neuroanatomically and functionally linked to the pineal gland. Projections of the trigeminal ganglion to the pineal gland mainly derive from the ophthalmic part,⁷ and the ophthalmic branch of the trigeminal nerve represents the typical location of CH.

We have assumed that estimation of the IRF_{60} value (a measure of opioid receptor availability) by spectral analysis is valid for the pineal region, which is believed to be located outside the blood-brain barrier. Although factors such as agent delivery and [^{11}C]DPN metabolites may influence IRF_{60} values differently in intrabrain and extrabrain regions, we do not believe they contributed to the differences we observed between groups.

Because voxel-based morphometry has not demonstrated structural changes in the pineal gland,² the observed decrease in opioid receptor binding is suggestive of either receptor down-regulation or increased release of endogenous opioids (and competitive binding). Because opioids increase the secretion of melatonin⁵ and melatonin in turn alters beta-endorphin levels,⁸ opioidergic function in the pineal gland may relate to pathologic melatonin homeostasis in CH³ as well as to the therapeutic effect of melatonin.

Because episodic CH can evolve to chronic CH, it is generally assumed that episodic and chronic CH share pathophysiologic mechanisms. Our results cannot definitely answer whether pineal dysfunction is also present in chronic CH, but the diprenorphine binding of the patient with chronic CH points in this direction. Notably, we observed decreasing receptor availability depending on disease duration in the ACC, which is thought to be involved in descending pain modulating circuitries, and the hypothalamus (ipsilaterally to the CH). The hypothalamus is also well known as a part of the biologic clock. In rats, nocturnal melatonin supplementation decreases opiomelanocortinergic activity in the hypothalamus.⁹ In contrast, melatonin deficiency in CH may lead to an increased opioidergic function in the hypothalamus, which in the long term may cause a reduced availability of opioid receptors.

The CH patients in our study did not experience acute pain during the study or immediately before. It is therefore improbable that the alterations in opioidergic binding represent simple effects of acute pain processing. Rather, we suggest that opioidergic mechanisms, effective in the pineal gland and hypothalamus, are involved in the generation of CH attacks. This fact is also underlined by the observation that pinealectomy may lead to unilateral headache.¹⁰

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NeuroImages

Figure. Left deviation and irregular surface of the protruded tongue.

VIDEO

Infectious mononucleosis and unilateral tongue writhing

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A 9-year-old girl presented with isolated left hypoglossal nerve palsy secondary to infectious mononucleosis (figure). The left half

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of the tongue appeared in continuous movement (video). MRI and CSF revealed no abnormalities.

Denervation of muscles results in spontaneous activity, first described as “continuously rising and sinking, shining and twinkling, turning and burning, flowing and blowing” of the tongue after transection of hypoglossal nerves in dogs, more than one-and-a-half centuries ago.¹ The involuntary muscle contractions start after a few days and can persist for years.

Hypoglossal nerve palsy in association with infectious mononucleosis of young children is rare and considered to be inflammatory.²

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