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

Abstract—Using PET with the opioidergic ligand [11C]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 displays increased brain activity during attacks and structural changes have been evidenced in the same area by voxel-based morphometry. Neuromodulatory alterations point to participation of biologic clock generators in the pathophysiology of CH. Opioidergic changes and hypothalamic and cingulate alterations in CH have been suggested to be altered in CH, and oral administration of opioids can alter the secretion of melatonin by the mammalian pineal gland. 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 unpaired t test). Voxelwise negative covariation analysis of opioidergic binding projected in 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, and oral administration of opioids can alter the secretion of melatonin by the mammalian pineal gland.

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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.
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 structure 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, and the ophthalmic branch of the trigeminal nerve represents the typical location of CH.

We have assumed that estimation of the IRF₆₀ 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 [¹¹C]DPN metabolites may influence IRF₆₀ 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, 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 melatonin and melatonin in turn alters beta-endorphin levels, opioidergic function in the pineal gland may relate to pathologic melatonin homeostasis in CH 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. 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.

Figure 2. Scatter plot of the [¹¹C]diprenorphine PET binding (SPM-scaled impulse response function at 60 minutes [IRF₆₀] 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.

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References


NeuroImages

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 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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