Cluster headache and the hypothalamus – causal relationship or epiphenomenon?

A cefaleia em salvas e o hipotálamo – relação causal ou epifenômeno?

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Holle D, Obermann M. Cluster headache and the hypothalamus – causal relationship or epiphenomenon? Headache Medicine. 2012;3(4):188-97

ABSTRACT

Typical clinical features of cluster headache (CH) include trigeminal distribution of pain, circadian/circannual rhythmicity, and ipisilateral cranial autonomic features. This presentation led to the assumption that the hypothalamus plays a pivotal role in this primary headache disorder. Several studies using neuroimaging techniques or measuring hormone levels supported the hypothesis of a hypothalamic involvement in the underlying pathophysiology in CH. Animal studies added further evidence regarding this hypothesis. Based on previous data even invasive treatment methods such as hypothalamic deep brain stimulation (DBS) were tried for therapy. However, the principal question whether these alterations are pathognomonic for CH or whether they might be detected in trigeminal pain disorders in general in terms of an epiphenomenon is still unsolved. This review summarizes studies on hypothalamic involvement in CH pathophysiology, demonstrates the involvement of the hypothalamus in other diseases, and tries to illuminate the role of the hypothalamus based on this synopsis.

Keywords: Hypothalamus; Tegmentum; Deep brain stimulation; Headache pain; Pain generator; Voxel based morphometry; Functional imaging

RESUMO

Características clínicas típicas da cefaleia em salvas (CS) incluem a distribuição trigeminal da dor, o ritmo circadiano/circanual e as manifestações autonômicas cranianas ipsilaterais. Esta apresentação levou à hipótese de que o hipotálamo exerce um papel fundamental nesta cefaleia primária. Vários estudos baseados em técnicas de neuroimagem ou na medição de níveis hormonais apoiaram a hipótese de um envolvimento hipotalâmico na patofisiologia subjacente à CS. Estudos envolvendo animais acrescentaram evidências adicionais relacionadas a essa hipótese. A partir de dados prévios, foram tentados até mesmo métodos invasivos de tratamento, como a estimulação cerebral profunda hipotalâmica. No entanto, a questão principal – se essas alterações são patognomônicas para a CS ou se elas podem ser detectadas em transtornos dolorosos trigeminais em geral, na qualidade de um epifenômeno – está ainda não solucionada. Esta revisão sintetiza estudos sobre o envolvimento hipotalâmico na fisiopatologia da CS, demonstra o envolvimento do hipotálamo em outras doenças e tenta elucidar o papel do hipotálamo com base nesta sinopse.

Palavras-chave: Hipotálamo; Tegmento; Estimulação cerebral profunda; Cefaleia; Morfometria baseada em voxel; Neuroimagem funcional

INTRODUCTION

Cluster headache (CH) is a rare primary headache disorder that is characterized by strictly unilateral headache attacks accompanied by ipsilateral trigeminal autonomic symptoms such as lacrimation, rhinorrhea, conjunctival injection, tearing, facial sweating or ptosis.[1] As of its clinical presentation CH is classified as a trigeminal autonomic cephalalgia (TAC). Up to eight headache attacks occur per day often showing a strict time relationship with a nocturnal predominance of headache attacks.[1] Most patients have an episodic course of disease with a circannual periodicity of symptoms that occur mainly in autumn and spring. These clinical features suggested a pivotal role of the hypothalamus in CH. It was even

hypothesized that the hypothalamus could be the key "pain generator" in this primary headache disorder.

The current opinion about the role of the hypothalamus in CH is based primarily on a strong *a priori* hypothesis mainly in regard to the clinical picture. This review analyses the actual knowledge regarding the hypothalamus in the pathophysiology of CH and discusses whether these observations are specific for CH in terms of a "*primum movens*" or whether they might be just epiphenomena in pain/headache diseases in general.

As CH shares many clinical and pathophysiological similarities with other TACs in general (which are paroxymal hemicrania, short lasting unilateral neuralgiform headache attacks with conjuctival injection and tearing (SUNCT)) a particular comparison with these headache disorders will not be done in this review.

Table 1 - Clinical feature of cluster headache suggesting a hypothalamic involvement

Clinical feature	Explanation
Circadian periodicity	Headache attacks mainly occur on fixed times during day and night. The time of the day varies interindividually but is stable intraindividually
Sleep association	In most patients many of the headache attacks occur from sleep and awake the patients.
Circannual periodicity	Most of the patients report most of the CH episodes to start during spring or autumn
Ipsilateral cranial autonomic features	CH attacks are characterized by ipsilateral trigeminal autonomic symptoms such as lacrimation, rhinorrhea, nasal congestion, conjunctival injection, ptosis, facial sweating.
Trigeminal distribution of pain	Most patients report a supraorbital and/or temporal unilateral pain

THE HYPOTHALAMUS

Although the hypothalamus is only a small brain structure and contributes only to 0.5% of total brain volume[2] it plays a pivotal role in the human organism being involved in regulation of different biological systems that are essential for human survival (i.e. hormones, autonomic nervous system, temperature, emotional behaviour, arousal, cardiovascular system).[3]

Pain processing and autonomic nervous system

Interestingly, the hypothalamus is currently not considered to be part of the classical central pain processing network. However, there is emerging evidence that it might also be involved in central pain processing with predominantly antinociceptive effects contributing to descending pain modulation. The hypothalamus displays various ascending and descending connections to the nucleus tractus solitarius, rostroventromedial medulla, periaqueductal gray, raphe nuclei, and corticolimbic structures, which have an important function in the central pain matrix.[4] Despite this anatomical evidences there are also functional data pointing at the hypothalamus to take part in central pain processing. Stimulation of the hypothalamic medial preoptic nucleus (MPO) has antinociceptive effects on spinal cord neurons; after stimulation of the paraventricular nucleus which is also localized within the hypothalamus similar antinociceptive activations on hypothalamic subnuclei was detected.[5] Two hypothalamic neuropetides – orexin-A and orexin-B – also seem to play an important role in pain central pain processing of the trigeminal systems as they display pronociceptive and antinociceptive effects.[6]

Autonomic nervous system

The hypothalamus coordinates the interaction between autonomic function (facial nerve, parasympathetic outflow) and pain processing. The trigeminal autonomic reflex is thought to be involved in this connection, which is pictured by the clinical feature of trigeminal autonomic symptoms in trigeminal autonomic cephalalgias (TAC) in general, including CH.[7]

Circadian rhythms

The hypothalamus is often referred to as the "biological clock" as it is involved in several circadian patterns such as sleep- wake cycle, temperature, and hormonal regulation.[8] The main anatomic structure for chronobiological regulation is the hypothalamic suprachiasmatic nucleus (SCN).[9] Via direct neuronal connections the SCN influences various parts of the brain and induces, in turn, endocrine and autonomic functions.

CLINICAL PICTURE

The clinical presentation of CH has always been the foundation to allegedly proof the pathognomonic involvement of the hypothalamus in this disorder. However, other diseases share common clinical features that also suggest hypothalamic involvement. Many migraneurs report premonitory symptoms that precede the virtual headache attack up to two days and herald

the pain ahead.[10] The underlying pathophysiology of these premonitory symptoms which include irritability, craving for food, hunger, or tiredness are interpreted as clinical signs of hypothalamic dysregulation. Interestingly, most migraine attacks occur in the early morning, although this circadian rhythmicity is not as obvious as in CH patients.[11] In this context, a hypothalamic involvement has been suggested. Trigeminal autonomic features are a key clinical feature in CH, what also supports the hypothesis of a major role of the hypothalamus in the pathophysiology of CH. However, similar headache accompanying cranial autonomic symptoms can be also detected in many migraneurs during the headache, questioning the uniqueness of this clinical feature.[12] Other primary headache disorders do also share several important features of CH. Hemicrania continua (HC), a rare primary headache disorder, is characterized by strictly unilateral headache attacks accompanied by trigeminal autonomic symptoms. Hypnic headache (HH) patients share the characteristic time dependency and sleep association with CH. Some HH patients even report trigeminal autonomic symptoms.[13,14]

NEUROENDOCRINAL ABNORMALITIES

Neuroendocrinal abnormalities in CH

Many neuroendocrinological observations suggested an involvement of the hypothalamus in CH and suggested a deranged hypothalamic function. Inside bout a reduced plasma testosterone concentration was measured in male CH patients.[15] Imbalances of other hormones such as melatonin, cortisol, luteinizing hormone, follicle-stimulating hormone, prolactin, growth hormone, and thyroid-stimulating hormone, whose secretion is mainly controlled by the hypothalamus, have been detected.[16] These hormonal disturbances support the idea of a hypothalamic-pituitary-adrenal (HPA) axis malfunction in this primary headache disorder. Interestingly, changes of the CSF orexin level, which are considered to play a pivotal role in the pain processing of CH patients, were not observed during active CH episodes. Cavoli et al. measured orexin-A in ten patients with CH by radioimmunoassay. CSF Orexin levels were in normal range and no association between clinical presentation and orexin-A level could be observed.[17]

Several possbilities were discussed regarding the observed alterations. First, these changes may be result of the strong CH pain itself. Second, they may reflect a stress reaction (pain associated or independent) or, third, are induced by pain accompanying sleep disturbances. All of these possibilities would suggest that these alterations are rather unspecific phenomenon. Interestingly, some of the observed hypothalamic changes can be also detected in remission periods (i.e. CH outside bout) what would imply that these changes can be considered to be specific for CH itself continuing independently of the pain and therefore might be a kind of trait marker for the disease itself.

Neuroendocrinal abnormalities in other disorders

Even though endocrinal evidence suggests a strong involvement of the hypothalamus in CH, similar changes were observed in very different disorders as well. Chronic migraneurs show an abnormal pattern of hypothalamic hormonal secretion, such as a decreased nocturnal prolactin peak, increased cortisol concentrations, and delayed nocturnal melatonin peak. 338 blood samples (13 per patient) from 17 patients with chronic migraine and nine age and gender matched controls were analysed.[18] These observations question the exclusivity of hypothalamic involvement in CH.

A hyporeactive HPA axis similar to the changes observed in CH can be also detected patients suffering from fibromyalgia. Changes included disturbance of cortisol secretion (flattening of the circadian level, increased daytime levels in plasma and saliva) and increased nocturnal melatonin levels.[19] HPA axis alterations were also observed in chronic widespread pain,[19] chronic fatigue syndrome[20] and irritable bowel syndrome[21] (for meta-analysis of HPA axis activity in functional somatic disorders, see reference [22]).

GENETIC STUDIES IN CH

Children rarely suffer from CH. In these rare cases a genetic background is presumable as 2 to 7% have a positive family medical history for this disorder.[23] First-degree – relatives develop five to 18 times, second-degrees one to three times more often CH than the general population.[24] Genetic alterations within the orexinergic system of the hypothalamus were discussed to be responsible for this observation. It has been shown that the G1246A polymorphism of the OX_2R gene (HCRTR2) increases the risk for CH.[25] However, these data were not replicated in larger CH patient populations.[26] In migraineurs this gene polymorphism was not observed.[27]

CEREBRAL IMAGING: VBM, MRI, PET, SPECT

An increasing number of imaging studies was performed over the last year in CH. Although initial data were quite promising in detecting specific morphological changes in CH and distinct activation patterns, recent studies were often not able to replicate these findings or question the specificity of these observations for CH.

Structural imaging

Structural imaging of the hypothalamus in CH

One of the pioneer studies showing hypothalamic involvement in CH was performed by May et al. in the late 90ies of the last century. He used the method of voxel-based morphometry (VBM), that is an automated, unbiased, whole brain technique. It allows comparing structural brain images, especially regarding the volume or density of gray and white matter. May et al. investigated 25 CH patients compared with 29 healthy controls and detected isolated increased gray matter in the inferior posterior hypothalamus.[28] Because of the low prevalence of this headache disorder it took several years to repeat this investigation in a larger patient population and with newer probably more accurate analysis algorithm. Up to now, three studies were performed or are still ongoing, which did not confirm the initial finding. Matharu et al. investigated 66 patients suffering from CH, and 96 age- and gender-matched healthy subjects. This study did not detect any hypothalamic changes at all.[29] Similar findings were reported by two later studies.[30,31] Our own working group investigated 91 CH patients and failed to detect any hypothalamic changes. However, we were able to demonstrate several changes within the central pain-processing network.[30]

Structural imaging of the hypothalamus in other pain and headache disorders

An alteration of the hypothalamic gray matter in a similar area compared to the area described in CH was detected in hypnic headache (HH).[32] HH is a different rare primary headache entity that mainly affects elderly patients. Patients report strictly nocturnal headache attacks, mostly at the same time at night – that is why this headache disorder is also called alarm clock headache.[1] Interestingly, hypothalamic structural changes are even observed in diseases that do not share the sleep relationship as CH and HH do. Additionally, VBM and cortical thickness analysis showed an increase of hypothalamic gray matter in 11 patients with irritable bowel syndrome (IBS).[33]

Structural imaging of the hypothalamus in other diseases

Despite pain and headache disorders structural hypothalamic alterations can also be observed in other diseases without or with less prominent pain symptoms. Boghi et al. investigated 21 anorexic patients and 27 healthy control subjects using VBM. In the patient group they observed focal atrophy in the hypothalamus besides other changes. These changes correlated with the body mass index (BMI). The authors suggested that these hypothalamic changes point to hormonal dysfunction and central dysregulation of homeostasis.[34] Hypothalamic gray matter loss was also observed in 52 children and adolescents with autism. The authors contemplated that this alteration underlies the theory of dysfunction of the hormonal system in autism, mainly an alteration of oxytocin and arginine vasopressin.[35] Reduced hypothalamic gray matter was also found in boys suffering from fragile X syndrome.[36]

Several studies showed changes of the hypothalamus in patients with narcolepsy and cataplexy.[37,38] Narcolepsy is a sleep disorder, characterized by reduced hypocretin concentration in the cerebrospinal fluid. As hypocretin neurons are exclusively localized in the hypothalamus hypothalamic dysfunction was suggested.

Another VBM study showed gray matter atrophy in the area of the hypothalamus in patients with Huntington's disease.[39]

Functional imaging

Functional imaging in CH

Functional imaging allows picturing ongoing pain in the suffering brain in vivo. This technique thus offers a possibility to investigate acute pain processing and to figure out which anatomic structures might be involved. Nitroglycerine triggered headache attacks in nine chronic CH patients resulted in a strong activation of the ipsilateral posterior hypothalamus detected by $H_2{}^{15}O$ positron emission tomography (PET).[40] This activation pattern was also observed in spontaneous CH attacks in one patient who had undergone deep brain stimulation (DBS).[41] In four patients with episodic CH functional magnetic resonance imaging (fMRI) confirmed the activation pattern within the ipsilateral posterior hypothalamus.[42]

However, some authors suggested that the detected activation pattern in the functional imaging shows activation of an area only close to the hypothalamus, most likely the midbrain tegmentum.[43]

Functional imaging in other pain and headache conditions showing hypothalamic involvement

Hypothalamic investigation sometimes appears to be almost a pathognomonic feature in CH or TACs in general, but carefully crosschecking the literature does not confirm this first impression.

In several other pain disorders and even experimental pain conditions distinct hypothalamic activation during the acute pain state has been demonstrated suggesting that hypothalamic involvement might be a more general feature of pain itself.

In seven migraneurs without aura cerebral activations ($H_2{}^{15}O$ PET) were recorded during spontaneous migraine attacks without aura.[44] The observed activation pattern included several brainstem areas (bilateral ventral midbrain, dorsal contralateral midbrain in regard to the headache side, dorsomedial pons), cerebellum, frontal cortex, and cingulate cortex, which had been shown in prior studies. Additionally, activation of the bilateral hypothalamus was detected during the acute migraine attack. This activation pattern had never been described before. In contrast, further functional imaging studies studying migraneurs did not detect any hypothalamic activation.[45-47]

In HC an activation of the contralateral posterior hypothalamus was observed during acute pain exacerbation using PET.[48]

Twelve patients with angina pectoris were treated with intravenous dobutamine to elicit an acute sensation. Due to this pain experience the blood flow in the pain matrix and the hypothalamus increased.[49]

One patient who was implanted with a stimulation electrode within the left ventro-posterior medial thalamic nucleus because of a chronic facial pain was also investigated using functional imaging methods. The patient was measured when the stimulation electrode was working (without pain) and without stimulation (with ongoing pain). During the experience of pain significant increase of blood flow was observed in common areas of the central pain matrix and additionally in the hypothalamus.[50]

Hypothalamic activation is not only shown during pain disorders but can also be observed during experimental pain. Twelve healthy volunteers were stimulated with pain and warm sensations, which were applied to the left leg. Pain-related skin conductance reactivity was measured and association with fMRI activation pattern determined. Pain sensation activated several areas of the central pain processing system such as the anterior cingulate cortex, amygdala, and thalamus, but also in the contralateral hypothalamus.[51] In another PET study ethanol was injected intracutaneously in the right upper arm of four healthy volunteers to elicit acute traumatic nociceptive pain. Pain lead to a strong activation of the contralateral (left) hypothalamus.[52] Another study used the cold pressor test, which applies prolonged tonic painful cold stimulation to investigate pain associated activation pattern in healthy subjects. Additionally, cold non-painful stimulation was applied. Painful and non-painful sensations lead to an activity increase in brainstem and hypothalamic areas. Simultanously the galvanic skin response decreased. In line with the expectations the painful conditions induced a significantly stronger activation compared with the cold sensation.[53]

Resting state fMRI

The analysis of low-frequency (<0.1 Hz) fluctuations seen on fMRI scans at rest allows detection of functionally connected brain regions, so called resting state networks (RSNs). Synchronous variations of the BOLD signal can be measured as percentage signal change compared to the BOLD mean signal intensity over time.[54-56] The fluctuations observed by resting state analysis are thought to reflect the intrinsic property of the brain to handle the past and prepare for the future.[57] RS alterations were observed in chronic pain.[58] Rocca et al. studied RS in 13 patients with episodic CH compared with healthy controls. Patients were studied in a pain free state. Apart from other changes the authors observed functional connectivity within the network staring from the hypothalamus.[59]

Magnetic resonance spectroscopy

An additional exciting imaging technique to study brain biochemistry in vivo is magnetic resonance spectroscopy. In episodic CH patients hypothalamic N-acetylaspartate/creatine and choline/creatine levels are significantly reduced compared with healthy controls. Interestingly, changes were even detectable when the patients were outside bout, which means that they had no actual CH attacks anymore.[60,61] This observation led to the assumption that these alterations cannot simply reflect an epiphenomenon of pain itself.[61]

DEEP BRAIN STIMULATION: EVIDENCE OF HYPOTHALAMIC INVOLVEMENT IN CH?

The clinical picture of CH and the results from imaging studies provided the rationale for hypothalamic deep brain stimulation (DBS) in the treatment of CH. It was

though that this technique might offer a possibility to "turn off the CH generator" as high-frequency hypothalamic stimulation would inhibit hypothalamic hyperactivity.[62] The stimulation area was mainly chosen by adoption of the results from the initial VBM study.[28] To assess to what extent DBS stimulation is able to abort acute CH attacks Leone et al. investigated 136 CH attacks in 16 chronic CH patients.[63] Only 23 % of patients reported a reduction of pain intensity by more than 50%, and only 16% of headache attacks were completely terminated. These data indicated that DBS is not sufficient in the treatment of active CH attacks.[63] Further studies showed, that only continuous stimulation over several weeks markedly reduces or terminates CH attacks (for review [64,65]). Fifty-eight patients with chronic drug resistant CH and posterior hypothalamic DBS have been documented in literature, yet. Leone et al. investigated 16 drug-resistant chronic CH patients who received hypothalamic implants over a mean period of four years. After the first two years 83.3% of patients had experienced a pain termination or at least major pain reduction. After four years, still 62% of patients were pain free.[66] These results were confirmed by several other studies.

Interestingly, there were no changes in regard to long-term stimulation in electrolyte balance, sleep-wake cycle, or hormone levels of cortisol, prolactin, thyroid hormone, thyroid-stimulating hormone, which were accused before to be involved in the occurrence of CH attacks.[62,66-73]

Although the evidence of the imaging studies seemed to be overwhelming, some authors raised the question of the precise anatomical localization of the DBS. Sanchez del Rio and Linera questioned if the shown diencephalic/midbrain activity pattern corresponds rather to the midbrain tegmentum than to the genuine hypothalamus.[43,74] Although the anatomical boundaries of the hypothalamus are quite clear (anterior: lamina terminalis; posterior: posterior margin of the maxillary bodies; superior: hypothalamic sulcus; medial: third ventricle; lateral: subthalamus and internal capsule; inferior: optic chiasm, median eminence, tuber cinereum, mammillary bodies, and posterior pituitary), the functional boundaries are more vaguely determined.[75] Matharu et al. re-examined the statistical parametric maps and coordinates of the activation pattern of PET studies in CH.[74] The observed activation in the diencephalon and the mesencephalon in CH are centered over the midbrain tegmentum and are close to the hypothalamus but more anterior.[40] In contrast, functional imaging studies in CH using BOLD-fMRI studies detected activation of the posterior and middle hypothalamus rather than the mesencephalon. The authors suggest that these differences are most likely based on methodological issues, mainly the problem of insufficient spatial resolution (fMRI 4 to 5mm; PET 5 to 10mm). They conclude that these data can only be interpreted in the context of other knowledge, but might be, therefore, also influenced by a priori hypothesis. Moreover, stimulation of the trigeminal pain processing network by greater occipital nerve (GON) stimulation in CH patients presented similar results in regard to pain reduction efficacy suggesting a rather unspecific role of DBS stimulation in CH.

Additionally, positive DBS results were also observed in other pain disorders, questioning the patho-physiological concept of specific hypothalamic alteration in CH and raising some serious concerns regarding their validity and specificity. Interestingly, hypothalamic DBS was also effective in treatment of symptomatic trigeminal neuralgia (TN) in five multiple sclerosis patients.[76] These patients had to be therapy refractory prior to electrode implantation. Beneficial effects in regard to pain reduction were observed in three of the patients even within the first 24 hours after implantation. Symptomatic TN seems, therefore, according to the opinion of the study authors, a possible area of application for DBS. As long as controlled studies are missing in this regard the results of such studies should be interpreted with caution and careless utilization should be avoided. However, one can conclude based on the reported study results that DBS of the posterior hypothalamus is not exclusively effective in CH but also shows beneficial effects in other pain conditions as well.

In contrast, there are also chronic pain conditions were hypothalamic DBS seems not to be effective. Franzini et al. reported on four patients with secondary neuropathic trigeminal pain (pain after resection of a posterior mandibular carcinoma, unspecified facial pain; pain after radiotherapy of a nasopharyngeal carcinoma; and no description) who did not experienced any relevant pain reduction after electrode implantation.[76] However, the reported patient population was inhomogenous with not comparable clinical features, which makes an interpretation of the study results difficult.

HYPOTHALAMUS: PRIMUM MOVENS IN CH OR ONLY PART OF THE CENTRAL PAIN-PROCESSING NETWORK?

Looking at the clinical features of CH with trigeminal distribution of pain, circadian/circannual rhythmicity, and

ipsilateral cranial autonomic symptoms in combination with the results from the many imaging studies the pathophysiological importance of the hypothalamus seems to be obvious and scientifically proven, but newer data question the pivotal role of the hypothalamus in CH. Particularly structural and functional neuroimaging studies supported the hypothesis of hypothalamic alterations being involved in the pathophysiology of CH.[28,41,42] These data seemed to be so conclusive that even invasive therapy methods such as DBS were used to directly influence the "hypothalamic CH generator". However, other contrary findings should be also taken into consideration before prematurely adopt this hypothalamic hypothesis. One major criticism about most of the interpretations from previous studies is, that the focus was directed almost exclusively at results that support the hypothalamic importance of the hypothalamus in CH, while other data were often neglected or rendered unimportant. It might be useful to take a step back and have a look at the whole picture, as this strong hypothesis driven research might have led us in the wrong direction.

Hypothalamic activation and structural changes can also be also detected in other primary headache disorders such as migraine,[44] hemicrania continua[48] chronic facial pain[50] and hypnic headache[32] and is not an exclusive feature in CH. Interestingly, hypothalamic changes can even be observed in totally different pain conditions such as angina pectoris,[49] irritable bowel syndrome[33] or even conditions that not involve pain at all such as anorexia nervosa,[34] autism,[35] fragile X syndrome,[36] narcolepsy,[37,38] and Huntington's disease.[39] However, most of the neuro-imaging studies that investigated pain disorders other than CH, did not observe any hypothalamic alterations. However, most of the CH imaging studies take the involvement of the hypothalamus *a priori* as a basis of their analysis, which allows reduction of the significance level. In contrast, most of the other studies that investigated pain disorders, did not predefine the hypothalamus as target anatomic region, what impedes the dectection of more subtle activation or structural change below the threshold of statistical significance.

The exact anatomic localization of the observed activations or structural alterations in CH has been discussed quite controversially in the past[43,74] in regard to the limitation of spatial resolution (PET: 2 to 7 mm; MRI 4 and 5 mm). Based on these methodological limitations, it was suggested that the observed activations might be localized in the midbrain tegmentum rather than in the hypothalamus itself. Taking the limitation of spatial resolution into consideration, PET and MRI seem to be not proper methods to distinguish anatomically between these two regions. This might challenge the validity of many neuroimaging results presented in regard to anatomic precision.

Although neuroendocrine[16] and genetic studies[25] detected changes in CH and also seem to point at hypothalamic changes, the specificity of these observations must be questioned. HPA axis disturbances can be also detected in fibromyalgia,[19] chronic fatigue syndrome,[20] irritable bowel syndrome,[21] and migraine,[18] genetic mutations were not reproducible.[26]

EXPERT COMMENTARY

Although the clinical picture of CH with trigeminal distribution of pain, circadian/circannual rhythmicity, and ipsilateral cranial autonomic features support the hypothesis of hypothalamic changes in terms of a specific CH generator as *primum movens*, more and more studies results, especially conducted in other pain conditions, question this hypothesis. Taking all current information together it seems to be much more probable that the hypothalamus is only involved in pain processing in general as part of a pain network.

Previous studies on this topic were often driven by strong *a priori* hypothesis and all results were only interpreted in the context of these hypothesis. We can mainly learn from this example that overly clear pathophysiological concepts of any particular disease evidently lead to overinterpretation and bias. As these interpretations even lead to invasive treatment methods, which may even jeopardize patients´ wellbeing, it seems mandatory to question even strong plausible hypotheses more often, because they might not explain the whole truth and might point future science in a wrong direction.

FIVE-YEAR VIEW

There is a need for investigation of the true pathophysiological background of CH, probably based on a more multi-causal concept, as research of the last ten years was at least partly misguided by the main focus on the hypothalamus in CH pathophysiology. Further research should concentrate on different structures other than the hypothalamus that might be involved in the pathophysiology of CH.

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Received: 11/28/2012
Accepted: 12/15/2012