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Pathophysiology of cluster headache: From the trigeminovascular system to the cerebral networks

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Abstract

Background: Despite advances in neuroimaging and electrophysiology, cluster headache's pathogenesis remains unclear. This review will examine clinical neurophysiology studies, including electrophysiological and functional neuroimaging, to determine if they might help us construct a neurophysiological model of cluster headache.

Results: Clinical, biochemical, and electrophysiological research have implicated the trigeminal-parasympathetic system in cluster headache pain generation, although the order in which these two systems are activated, which may be somewhat independent, is unknown. Electrophysiology and neuroimaging have found one or more central factors that may cause seasonal and circadian attacks. The well-known posterior hypothalamus, with its primary circadian pacemaker suprachiasmatic nucleus, the brainstem monoaminergic systems, the midbrain, with an emphasis on the dopaminergic system, especially when cluster headache is chronic, and the descending pain control systems appear to be involved. Functional connection investigations have verified electrophysiological evidence of functional changes in distant brain regions connecting to wide cerebral networks other than pain.

Conclusion: We propose that under the impact of external time, an inherited misalignment between the primary circadian pacemaker suprachiasmatic nucleus and other secondary extra- suprachiasmatic nucleus clocks may promote disturbance of the body's internal physiological clock, lowering the threshold for bout recurrence.

Keywords

Suprachiasmatic nucleus, cerebral networks, functional connectivity, electrophysiology, pain

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Introduction

Despite the advances in understanding cluster headache (CH) made with modern neuroimaging and electrophysiological techniques, a unified pathophysiological explanation of this primary headache is lacking. It is thus not surprising that discussion of the basis of the disorder continues. In this clarifying process, advances in genetics have further emphasized the role of certain brain structures, like the hypothalamus, yet many more questions remain unanswered (1,2).

What is certain is that this is a neurovascular headache, where activation, or the perception of activation, of nociceptive trigeminal nerve fibres and the craniofacial parasympathetic nervous system are *sine qua non* conditions for the clinical manifestation of the disease, i.e. pain and accompanying autonomic symptoms (3). The clear diurnal recurrence, as well as the seasonal recurrence, have inevitably given a pivotal pathophysiological role to pacemaker neurons in the hypothalamus. This role was supported by neuroimaging studies,

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where activation of the region of the posterior hypothalamus ipsilateral to pain in cluster headache was shown (4). Interestingly, the same activation was observed not only during pain in all other autonomic trigeminal headaches (5–7), but also before the onset of and during migraine pain (8,9), albeit in a different part of the structure. This inevitably reshapes the role of the hypothalamus as the sole site of primary dysfunction underlying cluster headache. Some suggestions come from a re-evaluation of neuroimaging studies of patients implanted with deep brain stimulators for the treatment of refractory forms and from more recent functional connectivity studies (10,11).

In this review, we will analyze clinical neurophysiology studies, which include electrophysiology and functional neuroimaging studies, to better understand whether the results found in the literature may allow us to create a neurophysiological model of cluster headache.

The trigeminovascular and parasympathetic systems

The hypothesis of the 1970s of an inflammatory process in the cavernous sinus and tributary veins ('venous vasculitis') underlying the pain and the damage of the parasympathetic fibres passing through it (12) was abandoned when neuroimaging evidence of its involvement in CH was observed also in patients with other pain syndromes such as Tolosa-Hunt, cervicogenic headache, migraine, and tension-type headache (13,14). This suggested that these changes in the cavernous sinus are an epiphenomenon of trigeminovascular activation rather than having a primary causative role.

The trigeminovascular and parasympathetic systems are anatomically and functionally interrelated. The cerebral vessels and dura mater are innervated by the pain producing fibres of the first division of the trigeminal nerve starting from the trigeminal ganglion. The same cerebral vessels are innervated by both sympathetic and parasympathetic fibres, which originate from the intermediolateral cell column in the thoracic spinal cord (15) and from the superior salivatory nucleus (SSN) in the pons (16), respectively. The efferent fibres travel along the facial nerve, through the geniculate ganglion, synapse in the sphenopalatine (SPG), otic, and carotid ganglia, and finally through the ethmoidal nerve to the cerebral vessels (17). Sympathetic and parasympathetic nerves get distributed around the facial area, innervating both the lacrimal glands and the glands of the nasal mucosa, providing the anatomical-functional basis for the symptoms lacrimation, rhinorrhoea, and nasal congestion (18) (see Figure 1). Experimental animal studies show that stimulating either between the Gasserion ganglion, the nociceptive craniovascular afferents of the SSN (with the greater superficial petrosal nerve as the efferent limb), and peripheral sensory fibres induce both release of vasodilatory molecules, including calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and pituitary adenylate cyclase-activating polypeptide (PACAP) at the peripheral level, and increased cerebral flow (19–23). Numerous studies have detected elevated levels of plasma and, even more so, tear fluid CGRP during attacks of cluster headache (24–26). However, CH attacks can be provoked by either PACAP38 or VIP without accompanied alterations of plasma CGRP or mast cell activation, downsizing the role of CGRP as the sole mediator of the attack (27). Nonetheless, stimulation of the first division of the trigeminal nerve can activate the parasympathetic reflex through the activation of parasympathetic neurons travelling the SPG (28).

Central nervous system mechanisms

There is debate as to why some patients may occasionally experience pain attacks without autonomic symptoms (29) or autonomic symptoms without pain (30). For some, the autonomic manifestation alone is due to the fact that the hypothalamus is anatomically connected to the SSN (31) and, therefore able to activate it without activating the trigeminal system (red pathway in Figure 1). Against this hypothesis is the evidence that when the deep brain stimulator (DBS) implanted in the posterior hypothalamus is switched on, ipsilateral activation of the trigeminal nerve and ganglion is observed, even though patients are free from pain (32). Although a nitroglycerin triggering study has shown cranial autonomic symptoms can be seen prior to the pain (33), it cannot be ruled out that the two systems, trigeminal and parasympathetic, work in parallel and activate at a threshold independent of each other, perhaps depending on the intensity and/or duration of pain (34). This would explain why patients with other primary headaches, like migraine, may also experience activation of the parasympathetic reflex during pain (35,36). The evidence in clinical cases of CH attacks even after complete sectioning of the trigeminal nerve (37) or attacks secondary to lesions of deep brain structures (38,39), further complicates the pathophysiological picture of CH, suggesting that peripheral activation of the trigeminal nerve is not sufficient to explain the pain in CH. These data were considered in favour of the hypothesis of multiple central permissive anatomico-functional factors underlying the pain and recurrence of cluster headache. The existence of these central factors is strongly supported by the fact that CGRP or nitroglycerin infusion in CH patients during the in-bout period can cause a CH-like attack

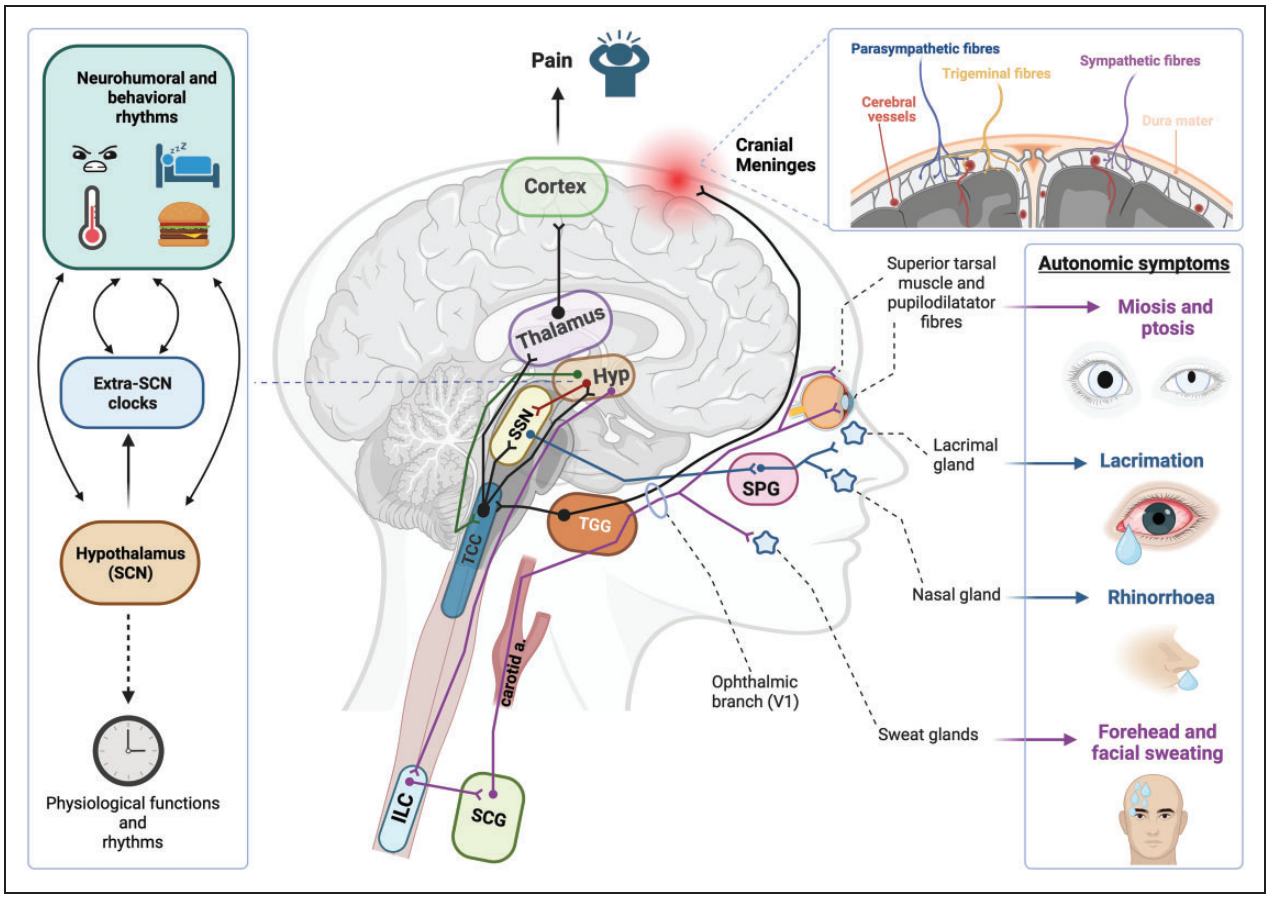

Figure 1. A neurophysiological model of cluster headache pathogenesis:
A. The hypothalamus regulates circadian and physiological rhythms through the suprachiasmatic nucleus (SCN), which also influences the various extra-SCN clocks. In addition, these clocks are influenced by neurohumoral rhythms (melatonin and temperature) and behavioural rhythms (food intake, sleep, emotions). On the basis of a predisposing genetic load, a dysregulation of the hypothalamus mediated by a change in neurohumoral and behavioural rhythms can lead to a dysregulation of melatonin production (sympathetic pathway) and trigger the attack by activating the connections with the trigeminal nucleus (trigeminovascular pathway) and the superior salivatory nucleus (parasympathetic pathway) activating the trigeminal autonomic reflex and triggering the attack.
B. Anatomical pathways and connections with autonomic symptoms: sympathetic pathway (a), trigeminovascular pathway (b), parasympathetic pathway (c)
a) the sympathetic pathway (in violet) is activated by the perception of light arriving from outside (not shown in the figure), which reaches the hypothalamus, from where axons depart and synapse with neurons in the lateral intermediate column (ILC) of the spinal cord (thoracic cord). The fibres emerge from ILC and through ventral roots of the corresponding spinal roots, passing to the ventral rami of the spinal nerve trunk and to the white rami communicantes, synapse with neurons in the lateral chain of the sympathetic ganglia and then with the superior cervical ganglion (SCG). The SCG give rise to non-myelinated postganglionic fibres, which arise as the internal carotid nerve and ascends with the internal carotid artery forming a plexus known as the carotid plexus. From the carotid plexus originates the oculosympathetic fibres and the sudomotor fibres. Oculosympathetic fibres, travelling near the ophthalmic branch of the trigeminal nerve (V1), reach the fibres of the dilator pupillae. Sudomotor fibres, passing through the supraorbital nerve (not shown in the figure), reach the skin and the sweat glands. Another contingent of the fibres originated from the SCG synapse with neurons in the pineal gland (not shown in the figure) that produces melatonin and thus controls circadian rhythms. Connections exist between the hypothalamus and the inferior salivatory nucleus (neuron in red) and between the hypothalamus and the trigeminal nucleus (neuron in green). Through these direct connections, the hypothalamus, when dysregulated (picture on the left showing the clock, i.e. the suprachiasmatic nucleus, and extra-SCN clocks) could directly activate the trigeminal autonomic reflex to trigger the attack.
b) The trigeminovascular system (in black) innervates, together with the sympathetic and parasympathetic systems, the dura mater and the cerebral vessels; the cell body of the T-neuron of the trigeminovascular system, located at the level of the trigeminal ganglion, contracts synapses with the second neuron of the pathway in the nucleus of the trigeminal complex (TCC), from here it sends an axon to the thalamus (3rd neuron) and subsequently to the cortex for pain perception. During the passage to this pathway, it sends axons that contract synapse with the superior salvatory nucleus for the trigeminal autonomic reflex (blue pathway), which involves, through stimulation of the lacrimal and nasal glands, lacrimation and rhinorrhoea, typical autonomic symptoms of cluster headache.

Continued.

but not in patients during the out-bout period (24,33). Interestingly, in the CGRP study the median time to onset of parasympathetic symptoms preceded median onset of head pain. These findings help to elucidate the chain of clinical events in CH and suggest that CGRP can cause parasympathetic outflow and precipitate bouts of cluster headache (24). Even though the pain is present every day, it was found that chronic CH patients had lower plasma levels of CGRP than episodic CH patients, likely as a result of its depletion in trigeminal afferents (25). This finding reinforces the idea that CGRP is not the only mechanism of headache initiation in CH.

Instead, central permissive mechanisms could play a pivotal role in favouring the activation of the trigeminal-parasympathetic system. Several electrophysiological studies related to pain processing, especially trigeminal, support this. Inconclusive results were obtained in episodic and chronic CH patients from studies using electrical or laser pulse stimulation of the superficial skin layers for the study of trigeminal or extracranial pain-related cortical evoked potentials (40–42). This may be due both to the heterogeneity of the patients enrolled (episodic and chronic together, with or without prophylaxis) and to intrinsic limitations of the method, which is probably unable to functionally explore the areas involved in CH pathophysiology.

Electrophysiology

A number of other studies suggest CH is accompanied by a general sensitization of pain processing, not limited to the trigeminal system, but spreading even at the spinal level (43). Researchers have found evidence of faster recovery rates of R2 blink reflex (BR) response in a pre-pulse inhibition paradigm (after supraorbital paired pulse electric stimulation), perhaps indicating reduced central opioid activity (44) in line with succeeding neuroimaging findings (45,46). Other authors observed increased responsivity of trigeminal processing on the affected side of the head compared to the unaffected side (47–49). These responses normalized during the remission period (50), again favoring the hypothesis of an in-bout central permissive factor. Repetition of the stimulus reduces the BR's amplitude and area, mimicking "habituation" from repeated exposure to harmless stimuli (51). CH patients had poorer habituation of both the conventional R2 and R3 BR components than controls (52). CH patients had even less habituation than episodic migraine (52). In episodic CH, after an initial hypo- (not hyper-) reactivity of the R2 reflex area, a delayed lack of habituation was detected on the headache side than on the non-headache side (53). Some authors found a frequency-dependent habituation deficit of the R2 component of the nociceptive (n)BR in episodic CH both during active and remission period (54). This abnormal temporal pattern of pain processing may indicate a trait-dependent dysfunction of some underlying pain-related subcortical structures, rather than a state-dependent functional abnormality due to the headache attacks during the active period. These reflex abnormalities may be related at least in part to descending aminergic (especially dopaminergic) control malfunction, as suggested by the evidence that rotigotine, a transdermal dopamine agonist, normalized baseline reduced habituation of the R2 nBR component in a drug-resistant chronic CH patient (55). Interestingly, prolonged transcutaneous supraorbital nerve stimulation, the same used to elicit reflex blinking, may prevent, instead of promote, episodic and chronic CH (56).

Studies have also consistently shown reduced thresholds of pressure pain, electric pain, nociceptive corneal reflex, and nociceptive flexor reflex (NFR) after the stimulation of the sural nerve on the symptomatic side relative to the asymptomatic side, in both episodic during active compared to remission and chronic CH (48,57–60). NFR response has also been used to verify potential abnormalities in the circadian activity of the nociceptive spinal system in CH, which is cyclic like CH attacks (59). The authors found significantly preserved circadian rhythmicity of the NFR threshold in episodic CH during both active and remission periods, but the nociceptive spinal system was sensitized during the active period, resulting in a phase shift of the normal circadian rhythmic variations. Chronic CH patients had no NFR threshold circadian rhythmicity (59).

Perrotta et al. (60) examined the descending conditioned pain modulation system in episodic CH patients during active and remission phases using a cold pressor test (CPT). Compared to controls and CH patients in

Figure 1. Continued
c) The parasympathetic pathway (in blue) originates from the superior salivatory nucleus (SSN), which can be activated by connections with the trigeminal system through the trigeminal autonomic reflex, but also by connections with the hypothalamus (neuron in red). From the superior salivatory nucleus originate axons that connect with the sphenopalatine ganglion (SPG). From these two ganglia originate axons that respectively innervate the salivary glands, causing lacrimation, and the nasal glands leading to rhinorrhoea.
SPG: Sphenopalatine ganglion; TCC: Trigeminocervical complex; ILC: Intermediolateral column (thoracic medulla); SCG: Superior cervical ganglion; SSN: Superior salivary nucleus; TGG: trigeminal ganglion; SCN: suprachiasmatic nucleus; Hyp: hypothalamus; Carotid a.: carotid artery. Created with BioRender.com.

remission, active CH patients had a lower temporal summation threshold, a measure of sensitization. Only during this phase, the CPT did not affect the temporal summation threshold (TST), nociceptive withdrawal reflex (NWR) threshold, or area. CH patients have a supraspinal pain control system dysfunction that depends on clinical activity and facilitates pain processing, predisposing them to CH attacks (60).

Contradictory results were obtained in CH when the integrity of the pre- and post-ganglionic non-myelinated C sympathetic fibres, which are responsible for the sudomotor skin response, has been studied by recording the sympathetic skin reflex (SSR). Experimental research has shown that the posterior hypothalamus or the mesencephalic reticular formation are likely the SSR's generators (61). Some researchers have noticed a prolongation of hand-recorded SSR on symptomatic sides compared to asymptomatic sides without any changes of amplitude (62). Others failed to discover any appreciable differences between the latencies and amplitudes of CH patients' hand and foot SSRs during attack and remission periods (62–64). Altiokka and colleagues (2016) found that by analyzing face SSR, CH sufferers, without specifying whether they were episodic or chronic, had SSR latencies that were significantly lower and amplitudes that tended to be lower on the symptomatic side compared to the asymptomatic side throughout the bout, outside of attacks (63).

Overall, electrophysiological research has revealed widespread anomalies in the trigeminal and extratrigeminal levels of pain signal processing. Most of these anomalies are evident only during the cluster phase, which is also characterized by deficits in the descending pain inhibition system, the monoaminergic, and the opiatergic tone. Only the trigeminal response's habituation deficit is absent both inside and outside of the cluster, which is most likely a sign of a trait's underlying malfunction. All these findings point to the existence of a central predisposing factor underlying CH.

The role of the hypothalamus- functional imaging. May and colleagues (4), scanning nine chronic CH patients with $H_2{}^{15}O$ positron emission tomography (PET) during nitroglycerin-induced attacks, were the first to show clearly inferior hypothalamic grey matter region activation ipsilateral to the headache side. Later, other authors confirmed these data in a spontaneous headache attack of a chronic CH patient during an ongoing $H_2{}^{15}O$ PET study (65). These seminal neuroimaging findings were considered strongly in favour of the involvement of the biological clock located in the hypothalamus, with its 'master clock' suprachiasmatic nucleus, in the pathophysiology of CH (66).

Notably, the hypothalamus was not the sole brain area to be active in these studies, since the CH attack-induced activation also increases in the thalamus (4,65,67), anterior cingulate cortex, in the insulae bilaterally (4,67), in anterior cingulate cortex (65,67), basal ganglia (67) and inferior frontal cortex (67), with the addition of a generic significantly increased blood flow in the internal carotid artery ipsilateral to the headache side (67). During nitroglycerin-induced attacks, both the hypothalamus and ipsilateral ventral pons showed higher cerebral blood flow in a region of interest-based analysis (68).

The hypothalamus in cluster headache might be characterized not only by a neuronal dysfunction but even by changes in the neural membrane lipids. This was shown by MRI spectroscopy studies (69,70) where in episodic (both during and out of the bout) and chronic CH patients researchers demonstrated that the N-acetylaspartate (NAA)(69), a marker of neuronal integrity, and Cho/Cr metabolite ratio (70) are reduced in the hypothalamus in comparison to controls (69). Grey matter density, as assessed with the voxel-based morphometric (VBM) analysis, was reported to be increased in bilateral hypothalamus, with similar results in patients examined during and outside the bout (71), a datum not confirmed by others in larger cohorts of patients (72,73).

Using PET with the opioidergic ligand (^{11}C)diprenorphine in seven CH patients (six episodic and one chronic) who are in bout but out of an acute attack, Sprenger and colleagues demonstrated a decreased tracer binding in the pineal gland (45). Furthermore, the authors found an inverse relationship between the duration of cluster headache and opioid receptor binding in the ipsilateral hypothalamus and bilateral cingulate cortices. The latter observation suggests that descending opioidergic mechanisms in the pineal gland and hypothalamus, the formed producing and the latter controlling melatonin metabolism, might be involved in the generation of cluster headache attacks.

The role of the hypothalamic suprachiasmatic nucleus (SCN), the well-known primary circadian pacemaker capable of regulating the physiological rhythms that take place over the course of a 24-hour period, including the sleep-wake cycle, the need for food, and the regulation of body temperature (74), has received particular attention precisely because of this. In addition to be involved in the pathophysiology of CH, the SCN has also been linked to other conditions such persistent insomnia and several psychiatric disorders (75). From experimental models (76), it was suggested that left and right SCN constitute two antiphase coupled oscillators, mutually interacting but coupled separately to sunrise and sunset to accommodate seasonal change in the daily pattern of external conditions, so-called

'split condition' (77). It is conceivable that because SCN efferents project ipsilaterally to their extra-SCN area targets (37) that may also be running on antipodal time (77). The paraventricular nucleus of the thalamus, the periaqueductal gray (PAG), and the locus coeruleus are all areas outside of the hypothalamus and related to the SCN via the PAG (79). In turn, the SCN receives signals from the intrinsically photosensitive retinal ganglion cell of the retina (79), critically important for the generation and maintenance of the split condition (77).

Nonetheless, the SCN master pacemaker synchronizes extra-SCN oscillators in the brain with each other and with external time (78). The hippocampus, amygdala, nucleus accumbens, caudate, putamen, substantia nigra, lateral habenula, and lateral ventral tegmentum have all been identified as secondary, extra-SCN clocks, often known as 'slaves', even though biological rhythms are typically lost after surgical resection of the SCN (78). The midbrain contains many of these regions.

Several studies have documented abnormal resting-state MRI functional connectivity changes in patients with episodic CH between the hypothalamus and cerebral areas belonging to the pain neuromatrix, predominantly involved in salience information processing, to which pain belongs, during and outside the attacks (pre-frontal cortex, anterior cingulate cortex, contralateral thalamus, ipsilateral basal ganglia, and the insula and the cerebellar hemispheres bilaterally) (80–86). When the researchers compared scans taken during the attack to those outside the attack, during the bout, they found increased functional connectivity between the hypothalamus and the anterior and posterior cingulate cortex, the inferior frontal gyrus, medial frontal gyrus, inferior parietal lobule, parahippocampal gyrus, and amygdala (82). Most of these areas belong to the default mode network.

The role of the cerebral networks

However, it should be highlighted that a number of other networks have been separately linked to the pathophysiology of CH. Compared to controls, CH patients during the in-bout phase outside the attacks showed either diminished or strengthened functional connectivity within the sensorimotor, visual (81), default-mode (87), temporal, frontal (84,87,88), and dorsal attentional (85,87) networks. In one study, CH patients scanned during the in-bout phase outside the attacks exhibited a significant change in functional connectivity of independent networks encompassing the right inferior frontal gyrus and left postcentral gyrus compared to the scans acquired during the remission phase (87). In the same study, authors detected intrinsic functional connectivity changes in all the previously mentioned large-scale networks in CH patients during both in-bout and remission phases compared to controls (87). This points more toward neuro-functional alterations that predispose to cluster recurrence than it does to attacks themselves. According to some studies, the intrinsic connectivity of specific regions that are part of networks correlate with specific clinical disease variables (81,85–87). This finding raises the possibility that there is a bidirectional relationship between the phenotype of clinical disease and the neuro-functional activity of the brain.

Scan results during the bout showed decreased connectivity of the hypothalamus with the medial frontal gyrus, precuneus, and cerebellum regions (83), as well as increased intrinsic connectivity within the frontal and decreased connectivity within dorsal attentional large-scale networks (87), in comparison to scans taken during the remission period. By taking into account these areas' functional correlates, we can postulate that during the bout, precisely because the hypothalamus initiates pain, it connects less, i.e. activates less, with areas/networks of the brain that could instead stop it, such as the cerebellum and frontal regions, with a descending inhibitory function of pain. Subsequently, when this frontal cortical mechanism is deactivated, the visual attentional alerting system is activated, a cognitive mechanism that we have already seen in patients with chronic migraine (89). Moreover, using a linear kernel support vector machine approach hypothalamic changes are important for automatic discrimination of the MRIs of patients with migraine versus cluster headache (90). Interestingly, verapamil responders CH patients exhibited a reduced grey matter cluster density in lobule VI of the cerebellum compared with non-responders, further expanding its known role in antinociception (91).

When the researchers compared scans performed during the remission period to those of healthy subjects, they found increased intrinsic functional connectivity of the ipsilateral attentional network to the pain side, the cerebellar network (85), the working memory network, the executive control network, and the default mode network (DMN) (88). These functional abnormalities of large-scale networks that are present during the remission period point to cognitive changes associated with worry about the possibility of attack recurrence and an overuse of internalization as a pain-controlling strategy. In fact, it has been demonstrated that in healthy people, mind-wandering from incoming nociceptive stimulations increased connection between regions of the executive control network and the DMN as well as regions of the salience network (92).

The pathophysiological role of large-scale networks may explain several functional anomalies that have

been previously detected by recording cortical potentials elicited by different sensory modalities. Only the affected hemisphere showed lower amplitudes of visual evoked potentials during the pain-free period (93,94). Patients with episodic and chronic types of CH were shown to have an asymmetry of brainstem auditory responses, either during or outside of an attack (95). During both the active and remission phases, alterations in intensity-dependent auditory evoked potentials, which reflect the bioavailability of serotonin centrally, were found (96). Additionally altered during and after the bout, particularly on the affected side, were lemniscal somatosensory evoked responses (97) and evoked potentials elicited peripherally by transcranial magnetic stimulation over the motor region (under GABAergic control) (98). The latencies of event-related cognitive evoked potentials were also observed to be differently altered during the active period compared to the remission period in CH patients, underscoring the multidimensional involvement of recurrent and severe pain such as CH (99–102).

These findings, combined with the hemodynamic data from the fMRI, suggest that CH patients may have widespread functional anomalies which may be, at least in part, explained by a number of neurotransmitters dysfunction, including dopamine, serotonin, and GABA.

The role of the midbrain

DBS of the posterior inferior hypothalamus was the first neuromodulatory technique to be proposed for the treatment of drug-resistant chronic CH, with its rationale based on the neuroimaging evidence of the involvement of this small area in the initiation and maintenance of a CH attack (4). However, revisiting the stimulation coordinates of DBS studies of the posterior hypothalamus, some researchers observed the involvement of the ventral tegmental area (VTA) within the midbrain (10,103), questioning the real site of action of DBS. Implantation of a DBS device in this region in patients suffering from CCH (104,106) and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) (107,108) can revert the chronic course of CH to episodic. This questioned the specific neurons important for CH. The ventral tegmental area (VTA), bilateral substantia nigra, sub-thalamic nucleus, dorsal nuclei of raphe, and red nucleus all showed greater functional connectivity with the ipsilateral-to-the-pain hypothalamus in chronic CH patients (109).

According to structural MRI research, chronic CH patients had larger volumes of the bilateral nucleus accumbens, ventral diencephalon, hippocampus, frontal pole, and right amygdala than healthy people (11). When compared to controls, the resting-state functional MRI data analysis on the same patients revealed significantly reduced functional connectivity in the right frontal pole-right amygdala pathway, suggesting that the prefrontal areas may have failed to modulate the mesolimbic structures (11). As mentioned above, one patient with drug-resistant chronic CH was successfully returned to episodic behaviour with the use of the transdermal dopamine agonist rotigotine (55,110). Overall, these findings prompted various researchers to hypothesize that the pathophysiology of CH, and specifically the process of its chronification, may be influenced by a dysfunction in descending aminergic control, particularly dopaminergic control.

It is generally known that the hypothalamus and the midbrain influence each other in both directions (111). Hypothalamic orexin cells are inhibited by dopaminergic VTA neurons (112), while being activated by the latter (113). Increased plasma levels of dopamine and other associated neurotransmitters (114) as well as a diminished growth hormone response to apomorphine in CH patients (115) provide additional evidence that the midbrain aminergic circuits are involved in the pathophysiology of CH. The serotonergic dorsal raphe nuclei of the midbrain, which are involved in the regulation of pain, are also a target of hypothalamic orexinergic neurons (116). It is debatable, though, whether the midbrain VTA and the serotonergic system are basic dysfunctions in the pathophysiology of CH or whether they are subsequent to the hypothalamic activation in response to stress.

Conclusions

Data reviewed here suggest that different neurons play a cooperative role in the pathophysiology of cluster headaches.

The analysis of a variety of pain-related and non-pain-related cortical and subcortical processes revealed lateralized functional abnormalities in all of them, particularly during the in-bout phase as opposed to the almost complete absence of abnormalities seen during the out-of-the-bout phase. In addition to the hypothalamus's prominent involvement in the attack and its altered functional connectivity with brain areas/networks, frequently of both hemispheres, related or not to the processing of salient multimodal information, such as pain, the activation patterns observed include brainstem responses both related to trigeminal and non-trigeminal pain, as well as responses related to a spinal sensitization process.

It is currently unclear how these intricate functional alterations tie into the pathophysiology of cluster headaches and how the processes behind them work.

With regard to both the parasympathetic and trigeminovascular systems, it is feasible to hypothesize that the posterior hypothalamus may function as a crossroads and hence play a significant role in activating the cascade of events leading to the headache episode. This is mostly due to the cluster period's known clocklike rhythmicity and to clusters' circannual cyclical recurrence. One hypothesis would be that a clock-secondary structure may at some time request to take over in place of the SCN master clock or try to function as an ectopic pacemaker. In this situation, the hypothalamus, via the activation of the SCN on the same side of the ectopic pacemaker, might physiologically engage the stress-response mechanisms, activate the trigeminal-parasympathetic alarm-signalling system, and ultimately initiate the pain before attempting to end it on its own (see Figure 1). Clusters owing to lesions outside the hypothalamus provide evidence for this pathophysiological hypothesis, and genetic research has linked numerous genes involved in the control of the hypothalamic clock to CH, including the CLOCK, NR1D1, PER, and cryptochrome genes (1,2,117,118). The nucleus accumbens, midbrain, and substantia nigra are examples of other brain areas that express the same genes and are locations of extra-SCN clocks (119–122). As with any disease model, modern working patterns and lifestyles are frequent sources of circadian misalignment, which encourages disruption of the body's internal physiological clock and lowers the threshold for bout recurrence (123).

The administration of any of transmitters, typically released in response to peripheral activation of the trigeminovascular system, are unable to induce attacks during the remission period, but only during the cluster period, and never in 100% of cases (24). This suggests that the trigeminovascular and parasympathetic systems appear to play a secondary role to that of the hypothalamus in this hypothetical pathophysiological model. Monoclonal antibodies against CGRP, indeed, have been found to be moderately effective in stopping this primary headache (124,125).

When an episodic cluster headache switches into a chronic condition, while CGRP levels fall to their lowest points (25) and pain-related electro-functional abnormalities and the subjective impression of pain intensity is largely within normal ranges, additional mechanisms may enter the picture. Invasive treatments like DBS may only be effective after weeks of the stimulator being switched on, i.e. due more to an indirect neuromodulatory effect on an area/network connected to it than a direct effect (126). The role of the hypothalamus in the period of chronification is undoubtedly to be scaled down. This is also because clinically the patient loses their characteristics of circadian recurrence of attacks. On the other hand, functional and clinical/electrophysiological connection investigations suggest a further role of the ventral midbrain tegmentum, particularly its dopaminergic projection regions, which, by theory, could become ectopic pacemakers, in the process of headache chronification.

There is still much to learn about this pathophysiological model in order to explain why pain is almost always strictly unilateral, why it has a completely unique quality from other headache pain, and why it can occasionally be of such an extraordinarily high intensity.

Article highlights

- CH's trigeminal and parasympathetic activation order is still debated.
- Electrophysiology and neuroimaging have identified central factors that may explain seasonal and circadian rhythmicity.
- The posterior hypothalamus, brainstem, and midbrain have been identified as major site of dysfunction.
- Neurophysiological data show functional changes in distant brain regions connected to wide cerebral networks.
- Hereditary misalignment between the primary hypothalamic circadian pacemaker and other secondary extra-clocks may play a prominent pathophysiological role.

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