*Review*

# Cluster Headache Pathophysiology—A Disorder of Network Excitability?

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**Abstract:** Patients' accounts of cluster headache attacks, ictal restlessness, and electrophysiological studies suggest that the pathophysiology involves Aδ-fibre nociceptors and the network processing their input. Continuous activity of the trigeminal autonomic reflex throughout the in-bout period results in central sensitization of these networks in many patients. It is likely that several factors force circadian rhythmicity upon the disease. In addition to sensitization, circadian changes in pain perception and autonomic innervation might influence the excitability of the trigeminal cervical complex. Summation of several factors influencing pain perception might render neurons vulnerable to spontaneous depolarization, particularly at the beginning of rapid drops of the pain threshold ("summation headache"). In light of studies suggesting an impairment of short-term synaptic plasticity in CH patients, we suggest that the physiologic basis of CH attacks might be network overactivity—similarly to epileptic seizures. Case reports documenting cluster-like attacks support the idea of distinct factors being transiently able to induce attacks and being relevant in the pathophysiology of the disorder. A sustained and recurring proneness to attacks likely requires changes in the activity of other structures among which the hypothalamus is the most probable candidate.

**Keywords:** sensitization; homeostatic plasticity; synaptic scaling; epilepsy

## 1. Introduction

Cluster headache (CH) is a primary headache disorder characterised by excruciating and strictly unilateral pain that, generally, centres near one eye [1,2]. During the attacks, which—if left untreated—may last up to three hours, most patients pace around restlessly with ipsilateral lacrimation, rhinorrhoea, and possibly other symptoms indicative of an increased parasympathetic innervation. In episodic cluster headache, which is the most common variant, attacks occur in bouts, which, on average, last about eight weeks and eventually pass into a remission period of variable duration. In chronic CH, attacks continue without remission [3,4].

Attacks occur spontaneously, but not randomly—the time of day, as well as age and sex, modulate the probability of their occurrence [5–7]. To understand the origin of the pain, researchers used imaging techniques—positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)—to track brain activity during the attacks [8,9]. They did not identify an attack generator but documented increased activity in the posterior hypothalamus, thalamus, insular cortex, as well as anterior cingulate cortex.

Interestingly, the processing of physiological nociceptive input implicates similar areas of the central nervous system, ref. [10] and the time of day as well as age and sex, are influencing factors, too [11–18].

In this review, we hypothesize that sensitization, as well as circadian changes in pain perception, autonomic innervation, hypothalamic activity—and possibly some other parameters—modulate neuronal excitability and force rhythmicity upon the disease (see Figure 1). The resulting hyperexcitability might then trigger spontaneous depolarization, which—favoured or prolonged by altered synaptic plasticity [19–21]—will result in excruciating pain. Hence, ill-regulated excitability rather than malfunctioning cortical structures might be the culprit of attack generation.
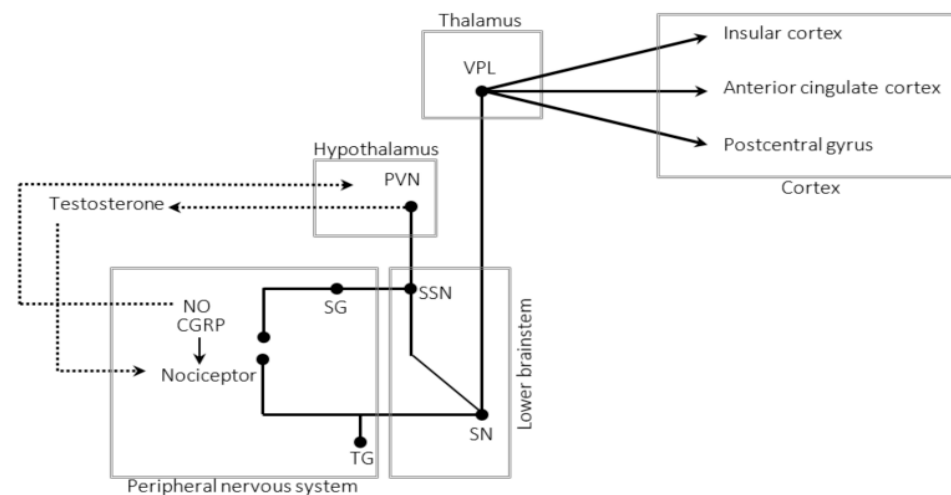


**Figure 1.** Summary of the different pain threshold-influencing mechanisms potentially implicated in the pathophysiology of cluster headache. The afferent part of the trigeminal–autonomic reflex runs through the trigeminal nerve and the trigeminal ganglion to the brain stem; the efferent part originates in the superior salivatory nucleus, runs through the facial nerve and the sphenopalatine ganglion, and modulates the release of CGRP and NO that lower the pain threshold (their concentration is increased in episodic cluster headache). The paraventricular nucleus of the hypothalamus also modulates pain perception possibly through its connection with the superior salivatory nucleus; this nucleus might relay the circadian rhythmicity of pain perception. Furthermore, testosterone (reduced during the active period of cluster headache) also influences pain perception possibly through modulation of nociceptors. Not depicted are pain-modulating descending pathways; their activity is influenced by melatonin (reduced concentration during the active period of cluster headache). Moreover, we did not depict the sympathetic nervous system that also has circadian rhythmicity. Please see text for further details. Solid lines depict anatomical connections; dashed lines refer to the action of hormones CGRP—calcitonine gene-related peptide; NO—nitrogen oxide; PVN—paraventricular nucleus; SG—sphenopalatine ganglion; SN—spinal nucleus of the trigeminal nerve; SSN—superior salivatory nucleus; TG—trigeminal ganglion; VPL—ventral posterolateral nucleus of the Thalamus.

We review the evidence supporting our hypothesis and discuss the idea in detail. It is our hope to contribute towards a better understanding of the pathophysiology of CH, and to stimulate new hypotheses for future studies.

## 2. Pain and Restlessness

Pain experienced in CH attacks resembles epicritic pain [22,23] because of its sharp, drilling or stabbing character, refs. [24,25] and therefore suggests an implication of the network handling nociceptive afferents from Aδ-fibre nociceptors. Interestingly, perceiving pain as epicritic might result in restlessness—a behaviour that usually accompanies CH attacks [22,26].

Epicritic pain feels like being inflicted by an exterior (and therefore escapable) cause; protopathic pain, on the other hand, appears to be related to an interior (and therefore inescapable) source [22]. Given that the former may lead to aggressive fight behaviour, and the latter to quiescence, the restlessness that often accompanies CH attacks may be a "fight

reaction"—an unconditioned reflex reaction to being threatened [22]. Conversely, the dull pain of migraine attacks might correspond to a protopathic type of pain, which leads to quiescence, and therefore the withdrawal of many patients.

In a rat model, distinct areas of the periaqueductal grey (PAG)—activated by sensory input from Aδ-fibre or C-fibre nociceptors—mediate behavioural responses to pain, which are restlessness and quiescence, respectively [27,28]. However, in a study using functional magnetic resonance imaging (MRI), no activation of the PAG was described during CH attacks [8]. Instead, there was increased activity in the posterior hypothalamus [8,9].

In humans, electric stimulation of the posterior hypothalamus can generate aggressive behaviour that may correspond to a fight reaction [22,29]. Consequently, ictal restlessness may be a form of human "fight reaction", ref. [22] caused by the resemblance of the attacks to epicritic pain caused by external stimuli.

### 3. Sensitization

Pain does not arise from the conscious realization of unfiltered sensory afferents—the nervous system modulates its afferents before the conscious mind becomes aware of them.

Sensitization amplifies pain caused by nociceptive input, ref. [30] and two types— peripheral and central—are distinguished, depending on whether it occurs in the peripheral or the central nervous system [30].

Peripheral sensitization results from factors mediating inflammation, the so-called "inflammatory soup", containing—amongst others—substance P, calcitonin gene-related peptide (CGRP), and tumour necrosis factor α [31]. Sensitization in the central nervous system results in increased responsiveness to nociceptive stimulation (hyperexcitability) and lowered thresholds for pain perception [30,32].

One possibility to quantify central sensitization is to measure the threshold and latency of the nociceptive flexion reflex (NFR)—a polysynaptic reflex that is mediated chiefly by Aδ-fibres [33,34]. Two studies using this method reported sensitization on the side of the headache during the in-bout period and—albeit to a smaller extent—during the out-bout period [35,36]. Notably, patients with chronic CH had no such finding compatible with central sensitization (see below).

Two studies measured the corneal pain threshold testing the nociceptive blink reflex in patients with episodic CH and a mixed sample of patients with episodic and chronic CH. They also reported bilateral sensitization that was more pronounced ipsilaterally to the attacks [20,37].

Quantitative sensory testing (QST) revealed lower thresholds for pinprick pain (mediated by Aδ-fibre nociceptors [18]) bilaterally on the back of the hand in the active period of CH; in the face, there was a trend towards a lower pinprick pain threshold [38]. Other pain thresholds (mediated exclusively or partly by C-fibre nociceptors [18]) were not affected. The presence of Aδ-fibre sensitization in skin areas not affected by the pain indicates so-called secondary hyperalgesia that is a correlate of central sensitization and the result of Aδ-nociceptor-activation [39].

Consequently, these studies suggest that the pathophysiology of CH attacks implicates networks processing Aδ-fibre input. Persistent pain between attacks and allodynia, which are prevalent among CH patients, refs. [40–42] indicate increased sensitivity. The chronology of central sensitization in CH is unstudied; in particular, we do not know whether sensitization precedes the bout or is a consequence thereof. However, given that so-called subsyndromal "shadow attacks" often herald the beginning of a cluster bout, ref. [43] we speculate that "full-blown" attacks occur when central sensitization increases.

### 4. The Influence of Prophylactic Treatment

Several drugs influence the frequency of CH attacks, and, interestingly, many of them raise the pain threshold and further support the idea of pain networks being central to the appearance of attacks.

Verapamil blocks N-type voltage-gated calcium channels (VGCC) that occur in presynaptic nerve terminals and play a role in transmitting painful stimuli [44]. In animal models, verapamil had analgesic effects that were probably chiefly due to a reduced release of neurotransmitters contributing to central sensitization [45,46].

Also, valproic acid sometimes reduces the frequency of CH attacks [47]; studies showed that treated animals had a reduced reaction to inflammatory and—to a lesser extent to—neurogenic pain [48–50]. Furthermore, melatonin raises the pain threshold possibly through modulation of descending pathways, refs. [51,52] and substitution prevented attacks in some patients with episodic CH [53,54]. No benefit was found in patients suffering from chronic CH [54,55].

Lithium often reduces the attack frequency in CH, refs. [56–58] and it attenuated allodynia for heat, cold, and mechanical stimuli in animal experiments [59–61]. Finally, animal studies on CGRP receptor antagonists suggest an impact on hyperalgesia, as well [62].

Topiramate seems to be an exception as it does not influence pain thresholds in the area of the trigeminal nerve, ref. [63] although it reduced the attack frequency in several—but not all [64]—studies [65–68]. Reduction in BOLD (blood oxygen level-dependent) activity in pain-processing areas like the thalamus, insular cortex, amygdala, mid-cingulate cortex, cerebellum and mesencephalon led to the hypothesis of the efficacy of topiramate being a consequence of its capacity to increase cerebral gamma-aminobutyric acid (GABA) levels [63,66,69].

Consequently, several drugs, which influence pain perception, seem to prevent attacks in both episodic and chronic CH, although one study reported no sensitization in chronic CH [36]. Thus, either influencing the pain threshold has therapeutic effects irrespective of sensitization, or these drugs have additional effects that help to prevent attacks.

## 5. The Trigeminal–Autonomic Reflex

Common symptoms of CH attacks, such as lacrimation and rhinorrhoea, as well as an increased serum concentration of vasoactive intestinal polypeptide (VIP) suggest elevated parasympathetic activity [70]. This increase results from an activation of the trigeminal–autonomic reflex, whose afferent fibres run in the trigeminal and efferent fibres in the facial nerve [70].

It is unknown which part of the reflex arc is activated first in spontaneous attacks; stimulation of neither part invariably leads to attacks [71,72]. The matter is further complicated by reports suggesting that the trigeminal nerve may not be necessary at all to suffer attacks [73,74]. Stimulation of the sphenopalatine ganglion, on the other hand, does prevent and abort attacks in many patients, suggesting that these nerve fibres do exert an influence on ictal pathophysiology and influence the probability of attacks [75].

Activation of the efferent reflex arc is associated with the release of neurotransmitters such as CGRP and nitric oxide (NO) [70,76].

Studies on CH attack frequency investigating the effects of antagonists directed against CGRP or its receptors yielded mixed results. While one substance met the primary endpoint in episodic CH, ref. [77] another did not [78]. In patients with chronic CH, these drugs produced no significant reduction in attack frequency, which is in contrast to the effects in chronic migraine, ref. [79] suggesting that the CGRP-system exerts a smaller influence on attack frequency in CH than in migraine. The lower concentration of CGRP in chronic than in episodic CH, ref. [80] suggests a reduced activity of the efferent reflex arc in these patients.

NO is a potent vasodilator capable of triggering CH attacks [81] and possibly inducing —if administered for a sufficiently long time—even bouts [82]. It is often released during inflammatory processes and leads to central sensitization [83–86]. Sometimes, inflammation suffices to induce pain of similar phenotype temporarily. Case reports documented an association of local inflammations, such as sinusitis, ref. [87] facial herpes simplex, ref. [88]

and herpes zoster in the ophthalmic division of the trigeminal nerve [89] with cluster-like attacks.

Treatment with warfarin led to remission in some CH patients, possibly by inhibiting NO production [90]. Corticosteroids, which are highly effective in preventing CH attacks, inhibit NO production as well [91,92]. However, since the effect of corticosteroids usually does not outlast the intake of the drug for extended periods, ref. [93] NO is likely a mediator in advanced stages of the pathophysiologic cascade—but not the attack generator itself.

Between the attacks, there is an elevated concentration of CGRP and products of NO in the blood and cerebrospinal fluid (CSF) of CH patients, respectively [70,94]. Given the short half-life of these molecules, we suspect that the trigeminal–autonomic reflex is permanently active—not just during the pain phase. Such an increased activity might cause aseptic inflammation and sustain sensitization [76,83].

Consequently, "shadow attacks", ref. [43] and autonomic symptoms preceding the attack, ref. [95] might increase sensitization until reaching the threshold necessary to activate nociceptors. Thus, if and for how long autonomic symptoms precede the pain phase might depend on the "baseline sensitization". It would be interesting to investigate the correlation between the time autonomic symptoms precede the pain, the extent of central sensitization, and the concentrations of CGRP and NO products in future studies.

Assuming that the efferent arc of the trigeminal autonomic reflex is less active in chronic than in episodic CH, we may also suppose that less NO and CGRP are released. However, data supporting this hypothesis are still lacking. If true, such a reduced secretion could explain why sensitization is present in episodic CH, but not in chronic CH [36].

An inter-individually differing activity of the reflex may have therapeutic implications as well. Guidelines recommend both sumatriptan and oxygen as an abortive treatment for CH attacks [96]. However, while sumatriptan aborts attacks in episodic and chronic CH equally well, oxygen is less effective in chronic CH [97].

In an animal model, oxygen and naratriptan reduced the flow of the lacrimal gland that stimulation of the superior salivatory nucleus had elicited, ref. [98] suggesting that both affect the efferent arc of the trigeminal autonomic reflex. However, triptans inhibit not only the efferent arc but also trigeminal input, suggesting an influence on the afferent arc, ref. [99] which has not been described for oxygen. Consequently, altering the activity of the efferent reflex arm might be less efficacious in chronic CH because of its relatively smaller importance in the pathophysiology of an attack.

These findings and considerations suggest that, in patients transitioning from episodic to chronic CH, the trigeminal autonomic reflex loses importance concerning attack frequency and attack generation. Consequently, changes in the pain threshold induced by reflex activity cannot be the only mechanisms contributing to the onset of an attack.

## 6. Circadian Rhythmicity

Several studies analysing pain perception reported circadian fluctuations with differing maxima for different types of pain [11–17]. The circadian rhythms of epicritic and protopathic pain are phase-shifted [17,100]; the detection threshold for epicritic pain is lowest at noon, while the threshold for the detection of protopathic pain is lowest at night with a minimum around midnight [100]. The mechanism regulating circadian changes in pain perception is not known.

Similarly, CH attacks do not occur randomly. In many patients, CH has circadian and circannual rhythmicity [101]. While the risk of an attack is lowest around noon, it reaches an interim high at 4 p.m. and rises to its maximum shortly after midnight (see Figure 2) [5].

Investigating circadian changes in the NRF, ref. [36] Nappi et al. reported the highest flexion reflex thresholds at midnight, and the lowest at 6 a.m. in patients suffering from episodic CH, suggesting a steep fall after midnight—similar to the circadian rhythmicity of CH attacks (see Figure 2). In chronic CH, however, they detected no circadian rhythmicity.
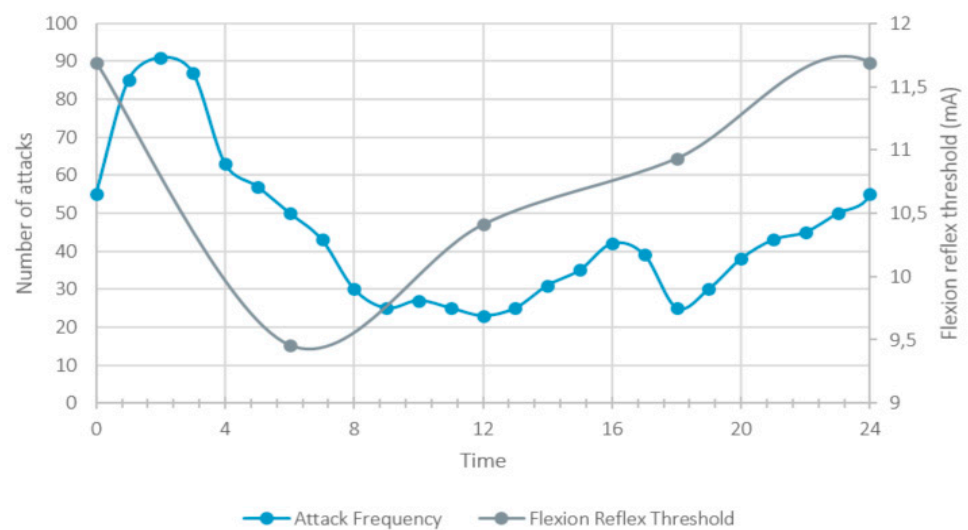
**Figure 2.** Correlation between time and attack frequency as well as time and the flexion reflex threshold in patients with episodic cluster headache; the The left vertical axis refers to the number of attacks in a sample of cluster headache patients,; the right refers to the flexion reflex threshold (mA). Data derived from Nappi et al. [36] and Barloese et al. [5].

Consequently, changes in the probability of occurrence of CH attacks parallel changes in the threshold for epicritic pain [11,14] These findings are compatible with the idea of shared neuronal networks processing epicritic pain and CH attacks, and suggest that circadian changes in the threshold of epicritic pain might be linked to the rhythmicity of CH attacks.

Furthermore, Figure 2 indicates that attacks occur most frequently when the pain threshold drops—not so much when it is low (by absolute values)—suggesting that relative changes in pain threshold might be more important than absolute values.

## 7. The Autonomic Nervous System

Autonomic symptoms precede attacks in almost half of the CH patients, ref. [95] and Horner's syndrome sometimes accompanies them [102]. Hence, an altered autonomic innervation is a hallmark of the disorder, but its significance is incompletely understood.

Postganglionic sympathetic lesions cause Horner's syndrome similar to what CH patients often experience during and sometimes in-between attacks [95,102,103]. Occasionally, interictal sympathetic dysfunction in the face also leads to Harlequin syndrome, characterized by reduced ipsilateral facial sweating and flushing [104].

Based on arteriographic findings, some authors hypothesized that ictal swelling of the carotid artery, possibly mediated by increased activity of the locus coeruleus, ref. [105] could damage or temporarily incapacitate sympathetic nerve fibres [106,107]. Consequently, Horner's and Harlequin syndrome would be a consequence of an attack, rather than its cause.

The authors of one article reporting an attack mimicking cluster headache (caused by a dissection of the carotid artery) implied that a sharp decrease in sympathetic innervation, can cause pain resembling that of a CH attack [108]. Consequently and given that sympathetic innervation may reduce the activity of Aδ-fibre nociceptors, refs. [109,110] a sudden reduction may render patients prone to experiencing pain similar to CH attacks.

Based on the cited case report, ref. [108] we speculate that a persisting sympathetic deficit, indicated by an enduring Horner's syndrome, may increase the probability of suffering CH attacks. However, there is no published evidence indicating whether the extent of the sympathetic deficit influences attack frequency or bout duration. As attacks did not persist in this patient, ref. [108] an autonomic deficit itself is insufficient to lead to sustained disease activity.

In addition to a local reduction in the sympathetic innervation during attacks, there is a physiological and systemic decrease in the sympathetic activity at night, when attacks most commonly occur [111]. Counterintuitively, the authors of a case series suggest that an even further reduction in the sympathetic innervation through sympathetic blocks may prevent and abort attacks [112]. Thus, it remains open for discussion whether these circadian changes have an impact on attack generation at all.

Changes in the heart rate variability indicate that circadian rhythmicity underlies the systemic parasympathetic activity. The parasympathetic tone decreases during the day and increases at night until shortly after awakening (see Figure 3) [113,114].

Reduced parasympathetic activity is associated with increased pain perception in men, but not in women [115]. Could these sex-related differences account for the differences in the circadian rhythm of CH attacks between women and men [6]? Could increasing parasympathetic innervation lead to a rapid decrease in attack frequency between 2 and 4 a.m. and between 5 and 6 p.m. (see Figure 3)?
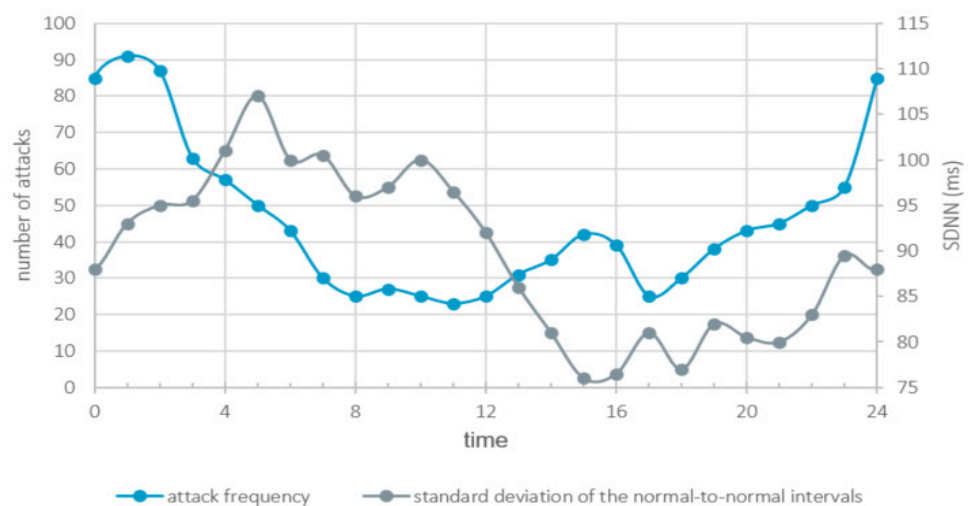


**Figure 3.** Correlation between time and attack frequency as well as time and the standard deviation of the normal-to-normal intervals (SDNN) in healthy adults; the left vertical axis refers to the number of attacks in a sample of cluster headache patients; the right refers to the standard deviation of the heart rate, which indicates parasympathetic innervation; data derived from Vandewalle et al. [114] and Barloese et al. [5].

One study reported a systemic reduction in the parasympathetic innervation both in-bout and out-bout [116]. This alteration might contribute to increased pain sensitivity.

In summary, a relative decrease in local sympathetic and systemic parasympathetic innervation is present in some CH patients and might influence pain perception. Little do we know about what causes these alterations of the autonomic nervous system; it can be hypothesized that the central nervous system—the hypothalamus being the most likely candidate—generates these long-lasting changes in pain perception and autonomic innervation.

## 8. The Hypothalamus

Changes in autonomous nervous system activity are not the only indications of the involvement of the hypothalamus in CH. Further arguments are (i) perturbations of the circadian rhythm of serum cortisol during cluster periods, ref. [117] (ii) a reduction in serum melatonin during cluster periods, refs. [117,118] as well as a (iii) reduction in testosterone—which leads to a reduced pain threshold [119] possibly through testosterone-sensitive TRPM8 receptors [120,121]—(iv) of prolactin, ref. [122] and (v) of TSH [123]. Moreover, fMRI studies showed decreased resting-state functional connectivity of the hypothalamus and an increased activity ipsilateral to the attacks [124–126]. Finally, the positive effect

on attack frequency of continuous hypothalamic stimulation may support the idea of hypothalamic involvement [126]. However, there are persisting doubts about the precise structures that stimulation needs to target to achieve therapeutic success [127,128].

The diversity of these findings suggests an implication of hypothalamic nuclei. A likely candidate is the paraventricular nucleus (PVN) that controls neuroendocrine and autonomic function, ref. [129] projects to the superior salivatory nucleus in rats, Ref. [130] and whose stimulation led to hypoalgesia in an animal model [131].

The PVN consists of magnocellular and parvocellular neurons; the former project to the posterior pituitary gland and influence the secretion of vasopressin and oxytocin; the latter provide superior control of the autonomous nervous system and secrete hormones controlling the anterior pituitary gland [129]. The above-listed studies reported reduced concentrations of several hormones that hint at a decreased activity of parvocellular neurons.

Interestingly, blocking NO led to an increased release of adrenocorticotrophic hormone and corticosterone in the PVN of rats, ref. [132] suggesting that an increase in NO—as seen in CH94—might do the opposite. Furthermore, NO donors applied to the PVN reduced the sympathetic innervation [133]. Consequently, the PVN can induce neuroendocrine changes similar to those seen in CH; NO donors, reported to induce attacks and bouts, refs. [81,82] could exert their effect in this area.

The paraventricular nucleus receives direct innervation from the suprachiasmatic nucleus that harbours the "inner clock" [134,135]. There are seasonal changes in the activity of this nucleus—but not in the PVN—which might contribute to the circannual activity of CH.134

Furthermore, this area might play a role in elevated body weight, and hypertension, ref. [136] which are slightly more common in CH patients than in controls [137]. The available evidence does not allow drawing definite conclusions, though; further research is necessary.

## 9. Homeostatic Plasticity and the Occurrence of Attacks

Several factors regulating pain perception are altered in CH patients, suggesting that their pain networks may be—intermittently or continuously—closer to depolarisation. Among these are sensitisation, a reduced autonomic innervation, as well as lowered testosterone, melatonin, and cortisol levels (see above). Moreover, depression [138] and sleep deprivation, refs. [139,140] which reduce the pain threshold as well, are also common [5,141]. Finally, circadian changes in pain perception also influence depolarisation probability.

Thus, in CH, there is a sustained decrease in the pain threshold—with additional super-imposed transitory decreases. Although the site of action is not precisely known for some of the implicated factors, it seems reasonable to believe that most influence nociception on the level of the brainstem and the peripheral nervous system (see Figure 1). Consequently, these factors modulate the firing rate of neurons signalling activation of nociceptors to the thalamus and cortex.

Studies reporting that stimulation of the trigeminal nerve or the sphenopalatine ganglion failed to elicit attacks in some patients during the in-bout period support the idea of several factors being necessary for an attack to occur [72,142].

We hypothesize that when the summation of several influencing factors maximally reduced the pain threshold, even weak activation of nociceptors might lead to the perception of intense pain with excitatory influences strongly outweighing inhibiting factors.

Neuronal excitability is generally tightly regulated because failure may lead to the synchronous firing of large numbers of neurons manifesting as epileptic seizures. For this reason, these controlling mechanisms—referred to as homeostatic plasticity—incited great interest among researchers in the pathophysiology of epilepsy [143].

The pathophysiological cascade of CH attacks outlined above implies network overactivity and malfunctioning of homeostatic plasticity in analogy to epileptic seizures. Interestingly, analysing habituation and the nociceptive blink reflex in patients with episodic

CH in- and out-bout, Perrotta et al. found evidence for faulty synaptic plasticity in CH patients, indicative of malfunctioning short-term depression (STD) [19].

Short-term synaptic plasticity influences the transmission of presynaptic action potentials to post-synaptic structures. Depletion of presynaptic vesicles, post-synaptic desensitization, and feedback activation of presynaptic receptors contribute to STD that limits transmission foremost at high depolarisation frequencies [144].

CH patients fail to habituate to high-frequency nociceptive stimuli, refs. [19–21] and commonly report rapidly increasing pain intensity during, on average, the first nine minutes of an attack [24]. Thus, there is neither electrophysiological nor clinical evidence of a short-term depression of synaptic transmission. On the contrary, the time course of pain intensity suggests potentiation.

Untreated attacks usually last between 45 min and 3 h [25]. It is possible that after this period, some threshold-lowering influences reduce their intensity, but the emergence of long-term depression is likely as well. A refractory period following attacks during which no attacks can occur spontaneously and whose duration correlates with the length of an attack, ref. [145] might indicate long-term changes in excitability. Moreover, the association of attacks with steep falls in the pain threshold—not with low thresholds in general—might imply that long-term depression prevents attacks but takes some time to set in. We are not aware of any study analysing long-term depression in CH.

While we do hypothesize that the depolarization of a network that processes input from Aδ-fibre nociceptors is common to all CH attacks, we also suspect that causal factors and their degree of influence differ between patients.

Lee et al. reported that circadian rhythmicity of the attacks occurs less frequently with an increasing number of bouts [101]. Thus, circadian changes in pain threshold become somewhat dispensable in the pathophysiology CH after some time suggesting attack-induced changes in other brain areas, possibly the hypothalamus. Moreover, the persistence of attacks in patients with chronic CH is intriguing given the absence of sensitization [36]. This implies that upon transitioning from episodic to chronic CH, proneness to depolarisation does not depend on sensitization anymore. Independence from sensitization may also explain why sectioning the trigeminal nerve does not prevent all patients from having attacks [73,74].

Furthermore, the occasional absence of autonomic symptoms [25] suggests that even increased parasympathetic activity may sometimes be dispensable.

## 10. Summary and Conclusions

Patients' accounts of CH attacks, ictal restlessness, and some electrophysiological studies suggest that the pathophysiology of CH involves Aδ-fibre nociceptors and networks processing their input. Continuous activity of the trigeminal autonomic reflex throughout the in-bout period might result in central sensitization within these networks in many patients.

It seems possible that an interplay of several factors allows for spontaneous depolarization and forces circadian rhythmicity upon the disease. In addition to sensitization, circadian changes in pain perception and autonomic innervation might be responsible for hyperexcitability of the trigeminal cervical complex (see Figure 1). It is likely that the relative importance of individual factors varies throughout the disorder—in particular when transitioning from episodic to chronic CH, or vice versa.

Summation of several factors influencing pain perception might render neurons vulnerable to spontaneous depolarization, particularly at the beginning of rapid drops of the pain threshold ("summation headache"). In light of studies suggesting an impairment of short-term synaptic plasticity in CH patients, we suggest that a key element in CH attack generation might be network overactivity—similar to epileptic seizures.

Case reports documenting cluster-like attacks are compatible with our idea of several factors being involved in inducing attacks. A sustained and recurring proneness to attacks could be explained by changes in the activity of supra-tentorial neuronal structures among

which the hypothalamus is the most likely candidate. The patterns of hormonal changes that commonly occur in CH patients support this idea.

Imaging studies provided evidence of network disruption and altered hypothalamic functional connectivity that back the idea of multifactorial disease [146]. Likewise, the effect of acute and preventive medication provides insights into the pathophysiology of the disorder [147]. However, these studies did not indicate where these alterations add together to trigger an attack. The strength of our hypothesis is that it indicates the attack generator more precisely than previous articles did.

Moreover, the predicted network overactivity may explain the excruciating pain that accompanies the attacks. Further, it might also explain the difference between very little to no pain during "shadow attacks" and excruciating pain, as only network overactivity would lead to intense pain. Finally, the strict unilaterality suggests that attacks originate from areas with little to no exchange of fibres representing different sides of the body such as the brain stem.

However, no study observed the predicted brain stem mechanisms (probably located in or mediated by the SSN or SN) yet. One approach to test the hypothesis could be the registration of the effects of repeated stimulation of Aδ-fibre nociceptors on functional imaging at different times. Based on the pathophysiologic mechanisms postulated above, we would expect that time determines the evoked brain stem activity.

Although we believe that much of the available data support our hypotheses, we need to mention some further limitations. The sample sizes in some of the cited studies were small, comprised mainly of men and not all researchers distinguished episodic from chronic CH. Furthermore, we cannot know whether the cited studies accidentally investigated subpopulations of CH patients that do not represent all patients. Some of the hypotheses presented in this article are speculative and await confirmation.

## Abbreviations

| | |
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| CGRP | calcitonin gene-related peptide |
| CH | Cluster headache |
| CSF | cerebrospinal fluid |
| fMRI | functional magnetic resonance imaging |
| GABA | gamma-aminobutyric acid |
| NFR | nociceptive flexion reflex |
| NO | nitric oxide |
| PAG | periaqueductal grey |
| PET | positron emission tomography |
| PVN | paraventricular nucleus |
| QST | quantitative sensory testing |
| SDNN | standard deviation of the normal-to-normal intervals |
| STD | short-term depression |
| VGCC | voltage-gated calcium channels |
| VIP | vasoactive intestinal polypeptide |

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