Introduction

Chronic daily headache (CDH) occurs in almost 2% of general population. Although CDH is the most frequent headache disorder observed in headache centers [1], it is not clearly classified by International Headache Society (IHS) diagnostic criteria [2]. The clinical variability characterizing CDH suggests that the underlying causes are heterogeneous.

The pathophysiology of chronic daily headache is still unclear. Clinical research of basic mechanisms is often inconclusive for the variability of the involved factors. Furthermore, there is a recent trend to use neurophysiological tests in the investigation of functional disorders in brain structures. In order to evaluate the pathophysiology of chronic daily headache, several methodologies have been employed. The aim of the present review is to relate the obtained results in the most frequently used neurophysiological tests to possible pathophysiological mechanisms of chronic daily headache. The neurophysiological findings suggest that a common neuronal dysfunction predisposes to primary headaches subtypes, whose chronicization may depend upon many factors, such as the influence of peripheral muscular factors and the dysfunction in central nociceptive modulation. These factors may explain the large variability observed in clinical features.

Key words Chronic daily headache • Neurophysiology • Evoked potential • Electromyography

Abstract The pathophysiology of chronic daily headache is unclear. Clinical research aiming to elucidate causative mechanisms is often confounded by the variability of factors involved. Furthermore, there is a recent trend to use neurophysiological tests in the investigation of functional disorders in brain structures. In order to evaluate the pathophysiology of chronic daily headache, several methodologies have been employed. The aim of the present review is to relate the obtained results in the most frequently used neurophysiological tests to possible pathophysiological mechanisms of chronic daily headache. The neurophysiological findings suggest that a common neuronal dysfunction predisposes to primary headaches subtypes, whose chronicization may depend upon many factors, such as the influence of peripheral muscular factors and the dysfunction in central nociceptive modulation. These factors may explain the large variability observed in clinical features.

Reflexology

Nociceptive flexion reflex

An objective method for measuring pain in humans is represented by the nociceptive flexion reflex (NFR). NFR has two successive components (RII and RIII). The RIII response is associated with pain sensation localized to the stimulation site. Nociceptive flexion reflexes are related to A-delta fiber activation. In normal subjects the value of the reflex threshold is strictly related to that of subjective pain perception.

Sandrini and co-workers [3] observed a reduction of RIII reflex threshold, strictly related to the severity of the
headache, in patients with migraine with interval headache (chronic almost daily headache).

In 40 patients with chronic tension-type headache (CTTH), Langemark et al. [4] found a high correlation between lower pain tolerance threshold and lower nociceptive flexion reflex threshold. These data confirm the hypothesis that chronic headache represents a disorder of endogenous antinociceptive systems. Indeed, a lower recruitment of descending inhibitory systems probably related to psychological factor may underlie the pathogenesis of CTTH [4].

**Exteroceptive suppression of temporalis muscle activity**

Exteroceptive suppression (ES) of muscular activity in the temporalis muscle is an inhibitory brain stem reflex that was applied for the first time by Schoenen in primary headaches [5]. After electrical stimulation of the mental nerve, early (ES1) and late (ES2) exteroceptive silent periods can be recorded over the temples during voluntary jaw occlusion. The second silent period was described to be decreased or abolished in up to 85% of CTTH sufferers [5], but ES2 abnormalities were unable to distinguish patients with chronic daily headache with drug misuse from those with CTTH, ETTH and migraine. This reflects the heterogeneous pathophysiology of CDH patients that evolves from tension-type headache, migraine, or a combination of both. Moreover, various pharmacological agents are able to modulate ES2 duration [6].

Other authors did not confirm these findings, probably for the variability of technical conditions: Gobel et al. [7] failed to detect ES2 abnormalities in a general sample of young chronic tension-type headache sufferers. Similarly, Zwart and Sand found no differences in the duration of ES2 in adult patients with either chronic TTH, migraine, or cervicogenic headache, relative to headache-free controls [8].

In a young adult population, Lipchik et al. [9] examined the ability of pericranial muscle tenderness and the second exteroceptive suppression period to distinguish chronic tension-type headache sufferers, migraine sufferers, and controls. In this study, TTH sufferers exhibited the highest pericranial muscle tenderness, while the shortened ES2 previously observed in adult patients with chronic tension-type headache was not evident in this sample of young headache sufferers. These findings raise the possibility that pericranial muscle tenderness is an early phenomenon in the development of tension-type headache, while ES2 suppression only emerges later in the evolution of the disorder.

In 32 females patients with CTTH, Schoenen et al. [10] observed that temporals ES2, pericranial electromyography (EMG) level and pain threshold abnormalities did not correlate with each other. These findings suggest that pain is not directly linked to muscle contraction while the reduction or abolition of temporalis second silent period is by far the most frequent pericranial abnormality in CTTH patients. This might be explained by the fact that both nociceptive mechanisms and muscular activity are involved in this electrophysiological test.

On the other hand, Nakashima and coworkers [11, 12] reported a decreased ES2 in idiopathic dystonia as well as in migraine without aura, and postulated that a low level of exteroceptive suppression is unspecific in patients suffering from chronic headaches. The attenuated or absent ES2 response was the major finding in chronic tension-type headache, although it was not confirmed by some researchers, probably for different methodological approaches.

The exact neurophysiological mechanism of the temporals silent period is not fully understood. It is still unclear whether abnormalities of ES2 in tension-type headache are primary or secondary to headache. The observation of a decreased ES2 duration in chronic pain syndrome without headache [13] suggests that this abnormality is not specific to TTH.

The two silent periods, the early inhibition (ES1) and the late second suppression period (ES2) are supposed to be mediated by separate neural nets in the pontobulbar lateral and medial tegmental fields which receive strong inputs from the periaqueductal gray, amygdala, hypothalamus, orbitofrontal gyrus and limbic structures [14]. These regions play a role in the modulation of nociception, so the duration of the late exteroceptive suppression period could be a marker for the functional state of the pain control system.

Schoenen [15] suggested that a disturbance of limbic pathways to the brainstem (a deficient activation or excessive inhibition) is the common factor underlying the various electrophysiological findings in chronic headache. The influence of neuropsychological factors on the inhibitory interneuronal function may be responsible for the great variability of the silent period duration [16].

**Blink reflex**

The blink reflex can give information on peripheral and central trigeminal functions. Electrical stimulation of the supra-orbital nerve, in fact, induces a reflex with two different components. The first component (R1), is a short latency response, ipsilateral to the stimulated side and transmitted via a pontine pathway. The second component (R2) is a bilateral, long-latency response mediated via a polysynaptic interneuronal pathway through the lateral reticular formation of the medulla. The R2 component that corresponds to visible closing of lids habituates quickly. A third bilateral
component of the blink reflex, R3, has been described by Penders and Delwaide [17]. This component has been found to be associated with nociceptive stimuli, to be inhibited by attention and to recover slowly. The relationship between R3 and pain is supported by the observation that R3 is markedly reduced by anesthetic block [18–20].

In migraine, some authors [21] have found an increase in R2 latency, but others [22] have not confirmed this finding. We evaluated the perceptive (Pth) and pain (Path) thresholds and the R1, R2 and R3 thresholds, latencies and amplitudes in 132 adult patients suffering from different forms of headache [23, 24]. The study population included 61 patients with migraine without aura, 10 patients with migraine with aura, 13 cases of episodic tension-type headache, 16 cases of CTTH, 13 patients with migraine without aura associated with tension-type headache and 19 others with headache that did not fulfill any IHS criteria. In addition, 15 young migraneurs were evaluated. As controls, 28 sex- and age-matched subjects were studied. Pth, Path and R1 and R2 thresholds, latencies and amplitudes were similar in all the studied subjects, whereas R3 distinguished patients from controls. The R3 component was triggered by stimuli of low intensity in headache patients, whereas it appeared only with painful stimuli in controls. Moreover, R3 amplitude was markedly higher in patients than in controls when over Path stimuli were used. The blink reflex R3 component was hyperactive in all patients, regardless of age or type and severity of headache (Figs. 1, 2). A dysfunction of the inhibitory pathways on the brainstem circuits may be responsible for the R3 hypersensitivity as well as for the physiopathological mechanisms predisposing to headache.

Fig. 1 An example of blink reflex recorded on the right side in a chronic tension-type headache patient. The electrical intensity was 5x perceptive threshold, enough to clearly elicit the R3 component. In this patient, the pain threshold was 12x perceptive threshold.
Methodologies for exploring muscular factors

The importance of pericranial muscles in headache is still unclear. The use of EMG, algometry and manual palpation has been proposed in the IHS classification for the evaluation of pericranial muscle disorders (third digit code) in differentiating patients with TTH or other headaches from healthy subjects.

Pain pressure threshold

Pain pressure threshold (PPT) is the threshold at which a pressure sensation becomes painful. Pain threshold in pericranial muscles was studied in a random sample of 735 adults by Jensen and Rasmussen [25]. In this study no significant differences were detected in the PPT at the anterior temporal region in patients with CTTH compared to the normal population or to other headache groups. Furthermore, a strong positive correlation between tenderness, evaluated by manual palpation, and frequency of TTH was found, while no relation between tenderness and migraine frequency was seen [26]. Further studies carried out in patients with CTTH reported PPT values in the temporal region not dissimilar from those detected in patients with ETTH or in healthy controls [27].

In other clinical trials, PPT was significantly decreased at frontalis and trapezius muscles in headache patients when compared with controls [28, 29]. Langemark et al. [28] showed that pain thresholds to heat and cold stimulation were significantly decreased in patients with CTTH compared to controls [28]. Furthermore, Schoenen et al. [29] confirmed a lower PPT in the frontalis region as well as over the Achilles tendon in patients with CTTH, in comparison with normal subjects [29]. These conflicting results may be due to different methodologies or to selection bias of headache sufferers: the patients with frequent but not daily headache, examined by Jensen and Rasmussen [25], may be less severely affected than patients with daily occurrence of headache, included in other studies. Although the PPT procedure in CTTH seemed able to relieve a generalized and multimodal increase in pain sensitivity, its usefulness for clinical purposes remains doubtful.

Electromyography

In order to evaluate the importance of tonic muscle contraction in the pathogenesis of primary headaches, EMG activity in pericranial muscles was assessed in several studies. Jensen et al. [30] performed quantitative EMG evaluation from the right frontal and both temporal muscles in 547 adults. In this study, 15 subjects with CTTH showed higher
amplitudes in their temporal muscles during rest in compari-
son with migraineurs, subjects with ETTH and subjects with-
out any experience of headache. In a further study, Jensen
[31] observed that EMG levels were unchanged during the
critical phase. The decrease in EMG levels during maximal
voluntary contraction observed in CDH patients suggests the
importance of peripheral factors such as morphological (rela-
tive type II fiber atrophy) and metabolic changes (accumula-
tion of metabolites) in headache chronicization.

Event-related potentials

Contingent negative variation (CNV) is a negative cerebral
potential, first described by Walter et al. [32], recorded over
the scalp. CNV is related to attention and arousal, and is
modulated by the central catecholaminergic system. The
early component of CNV is dependent on noradrenergic
activity (arousal), while the late component is modulated by
dopamine (activation).

In a previous study, Schoenen et al. [33] showed an
increase in the early component amplitude and a reduced
habituation in migraine patients, compared to controls or
patients with TTH. On the other hand, Gerber and Schoenen
[34] found normal CNV amplitudes and normal habituation
in migraineurs during the migraine attack. The normalization
of CNV may be due to a depletion of central noradrenergic
stores (noradrenergic arousal system) which reduces the
threshold for a migraine attack; alternatively it may be due to
a reduction of attention during the headache attack [35].

In a recent study, during a 3-s interstimuli interval,
amplitude and habituation of total CNV and of post-imper-
avative negative variation (PINV) were calculated in 15
women suffering from migraine without aura, in 15 women
diagnosed with CDH evolved from migraine without aura
with interparoxysmal CTTH, and in 15 healthy women [35].
In this study, according to previous observations [33, 36],
migraine patients were characterized by a more pronounced
negativity of the early component and total CNV, compared
to CDH sufferers and controls. CDH patients evolved from
migraine showed a reduced negativity of the late component
and a pronounced PINV compared to migraineurs and
healthy subjects, while both patient groups showed reduced
habituation of the early CNV component. The former abnor-
mality, observed in major depression and anxiety disorders,
may be due to the worsening of disease while the latter fea-
ture, independently from the clinical course of disease, may
be a basic characteristic of migraine brain [37]. The authors
concluded that CNV features may be predictive of trans-
formed migraine.

Discussion

The use of neurophysiological procedures in chronic daily
headache can contribute to confirm disorders in pericranial
pain sensitivity and/or possible abnormalities in central pain
modulation. Nevertheless, results obtained by neurophysi-
ological methods suffer from some methodological limita-
tions due to patient selection bias and variability in technical
procedures.

The results from studies of blink reflex, evoked potentials
and event-related potentials confirm the existence of central
dysfunctions predisposing to migraine as well as to TTH.
Schoenen hypothesized exclusively a central mechanisms
underlying TTH chronicization, on the basis of the decreased
exteroceptive silent period in patients with CTTH [5]. The
abnormal ES2 responses observed in CTTH may reflect an
excessive inhibition of brainstem interneurons secondary to a
disturbed limbic control structures such as the periacqueduc-
tal gray and raphe magnus nucleus. Moreover, CNV features
may be predictive of transformed migraine.

A purely central hypothesis fails to explain the relation
between headache and peripheral factors. Jensen et al. [30]
suggested that the chronic accumulation of metabolites due
to a persistent involvement of the pericranial muscles
explains the EMG findings in patients with CTTH [38, 39].
Indeed, involuntary contraction of muscles, due to a mechan-
ical or psychological stress, causes increased peripheral input
from mechanoreceptors and afferent fibers. A peripheral
mechanism of TTH can explain episodic subtype, whereas a
secondary, segmental central sensitization and/or an impaired
supraspinal modulation of incoming stimuli seems to be
involved in subjects with CTTH. Prolonged nociceptive stim-
uli from myofascial tissue may be a fundamental factor in the
conversion from episodic to chronic TTH.

Neurophysiological findings suggest that a common
neuronal dysfunction can predispose to primary headaches
subtypes, whose chronicization may depend upon many fac-
tors, such as the influence of peripheral muscles and a dys-
function in central nociceptive modulation. These factors
may explain the large variability observed in clinical features.
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